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Synthesis, characterization and study of novel reagents for the detection of saccharides and amino acids

Nadia Nadette St. Luce

Louisiana State University and Agricultural and Mechanical College, nstluc1@lsu.edu

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**SYNTHESIS, CHARACTERIZATION AND STUDY OF NOVEL REAGENTS
FOR THE DETECTION OF SACCHARIDES AND AMINO ACIDS**

A Dissertation

Submitted to the Graduate Faculty of the
Louisiana State University and
Agricultural and Mechanical College
in partial fulfillment of the
requirement for the degree of
Doctor of Philosophy

in

The Department of Chemistry

By
Nadia N. St. Luce
B.S., University of the Virgin Islands, 1999
May, 2004

DEDICATION

I dedicate this dissertation to Lucinthia St. Luce. Thank you for being a wonderful mother; for giving me life, unconditional love, support, education, guidance, prayers and most importantly the freedom to make my own decisions. You have always been my source of strength and inspiration. I love you very much and I hope I have made you proud.

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First and foremost, I would like to thank God without whom none of this would be possible. Next, I would like to give my deepest thanks to my research advisor, Dr. Robert Strongin, for affording me the opportunity to work in his group. Thank you for guiding me in my research and for always being there to help and support me. I would also like to thank the members (past and present) of the Strongin Research Group especially Jorge Escobedo and Oleksandr Rusin for your willingness to always help me. Very special thanks to Rolanda Johnson, with whom I started and completed the doctoral program. Your unreserved friendship, support and encouragement made weathering the storms of graduate school much more bearable. Thanks for the directory and location information, the long talks on the phone (especially about SAM), the adventures we shared and the great trips we took together and for staying by my side during my health crisis. Most of all, thanks for always being there when I needed you the most. I love you. Thanks Mohammed Sherriff and Matthew Morbe for your friendship. Special thanks, to Dr. and Mrs. Isiah Warner for your constant support, and belief in me. I would like to thank Dr. Dale Treleven, Dr. Frank Fronczek and Dr. Crowe for all their help on my research.

To my honey, Chideha Warner, thanks for bringing laughter and happiness into my life. You complete me, and my heart belongs to you. Mr. and Mrs. Rice; thank you for always being there for me, for your love, support and acceptance. Papa, thank you for all you have done for me. To my brother Janah, thank you for your companionship and support. To my baby brother, Kimo, you are the apple of my eye. Naomi thank you for

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LIST OF ABBREVIATIONS

amu	Atomic Mass Units
BHT	Butylated hydroxytoluene, 2,6-Di- <i>tert</i> -butyl-4-methylphenol
^{11}B NMR	Boron-11 Nuclear Magnetic Resonance
$^{\circ}\text{C}$	Degrees Celsius
calcd	Calculated
CCl_4	Carbon Tetrachloride
CDCl_3	Dueterated Chloroform
$\text{C}_6\text{H}_5\text{Cl}$	Chlorobenzene
CHCl_3	Chloroform
CH_2Cl_2	Dichloroethane
CH_3CN	Acetonitrile
CH_3OD	Dueterated Methanol
CH_3OH	Methanol
^{13}C NMR	Carbon-13 Nuclear Magnetic Resonance
$(\text{CH}_3)_4\text{Si}$	Tetramethyl silane
$\text{CH}_3\text{SO}_3\text{H}$	Methanesulfonic acid
$\text{CH}_3\text{SO}_2\text{H}$	Methanesulfinic acid
CH_3SOH	Methanesulfenic acid
COSY	Correlated Spectroscopy
DCE	1,2-Dichloroethane
DCM	Dichloromethane

D₂O	Deuterium oxide
DMSO	Dimethyl sulfoxide
EtOAc	Ethyl acetate
EtOH	Ethanol
FAB	Fast Atom Bombardment
FT-IR	Fourier Transform Infrared
g	Grams
h	Hours
HCL	Hydrochloric acid
HEPES	4-(2-Hydroxyethyl)-1-piperazineethanesulfonic acid
H₂O	Water
H₂O₂	Hydrogen Peroxide
HPLC	High-Performance Liquid Chromatography
¹H NMR	¹ -d Proton Nuclear Magnetic Resonance
HRMS	High-Resolution Mass Spectrometry
H₂SO₄	Sulfuric acid
LOD	Limit of Detection
<i>M</i>	Molar (moles/Liter)
<i>mM</i>	Millimolar (mmoles/Liter)
MgSO₄	Magnesium Sulfate
MALDI	Matrix-Assisted Laser Desorption Ionization
MeOH	Methanol
mg	Milligrams

mL	Milliliters
mmol	Millimoles
MS	Mass Spectrometry
MW	Molecular Weight
NaBH₄	Sodium Borohydride
NaBH(OAc)₃	Sodium Triacetoxymborohydride
Na₂CO₃	Sodium Carbonate
NaHCO₃	Sodium Bicarbonate
Na₂SO₄	Sodium Sulfate
NBA	N-Bromoacetamide
NMR	Nuclear Magnetic Resonance
O₂	Oxygen
OH	Hydroxide
ORTEP	Oak Ridge Thermal Ellipsoid Plot
³¹P NMR	Phosphorous-31 Nuclear Magnetic Resonance
P(OEt)₃	Triethyl Phosphite
ppm	Parts Per Million
PTZ	Phenothiazene
R_F	Ratio to Solvent Front
rt	Room Temperature
S/N	Signal to Noise
TLC	Thin-Layer Chromatography
TMSBr	Trimethylsilyl bromide

T_R	Retention Time
μM	Micromolar (micromoles/Liter)
UV	Ultraviolet
UV-Vis	Ultraviolet-Visible
$ZnCl_2$	Zinc Chloride
λ	Wavelength

ABSTRACT

The design of synthetic receptors for the recognition and sensing of saccharides and amino acids is currently a major challenge. This is due to inherent structural similarity and a lack of chromophoric or fluorophoric properties of these compounds. The synthesis and study of novel detection agents for bioactive molecules as well as mechanistic studies are presented herein.

The elucidation of the mechanism by which tetraarylboronic acid resorcinarene interact with sugar molecules and promote a solution color change is explored. This vast collaborative study, reveals that DMSO solutions of boronic acid functionalized resorcinarene macrocycles afford visual color changes upon heating or standing and in the presence of saccharides. We found that the solution color is due to macrocycle ring opening and oxidation. Condensation reactions catalyzed by acid formed in situ from DMSO are responsible for xanthene dye formation.

As a result of our mechanistic knowledge we were able to design and synthesize a variety of novel receptors. To date two selective receptors for the purpose of saccharide sensing have been synthesized. The first is a rhodamine-derived boronic acid receptor, for use in a novel post-column chromatographic procedure for the detection of saccharides. The second involves the designed and synthesis of a fluorescein-derived phosphonic acid receptor, which interacts with saccharides amino acids and anions via metal complexation.

As an extension of our work with saccharides we are exploring the detection of amino acids. We have discovered a highly selective new method for the facile determination of cysteine and homocysteine via a fluorescein dialdehyde derivative. In

addition, we have made progress towards the selective, direct colorimetric and fluorometric differentiation between cysteine and homocysteine in the presence of each other despite their great similarity in structure.

CHAPTER 1

INTRODUCTION

1.1 Discovery of Resorcinarenes

While studying the synthesis of phenol-based dyes, Adolf von Baeyer^{1.1} discovered a new class of compounds later known as resorcinarenes.^{1.2} He reported a reddish product and a crystalline compound, which was found later to be an isomer of the reddish product, was obtained when benzaldehyde was mixed with resorcinol in the presence of sulfuric acid. It was also noted that the reddish material turned violet in the presence of base. In 1883, the elemental composition of the product was determined by Michael^{1.3} to be $(C_{13}H_{10}O_2)_n$. According to his studies, the product was formed by reacting an equimolar amount of resorcinol and benzaldehyde followed by loss of an equal number of moles of water. Still unknown however, was the correct composition, which was determined by Nierdl and Vogel^{1.4} in 1940. Their studies of several condensation reactions involving aliphatic aldehydes and resorcinol led to the conclusion that the ratio between resorcinol and benzaldehyde to form the product was 4:4. As a result, Nierdl and Vogel proposed the product to be a cyclic tetramer (**1.1**) similar to those found in nature such as porphyrins. The structure was later proven by Erdtman in 1968 by X-ray analysis (Figure 1.1).^{1.5} The name "resorcinarene" was recently suggested by Schneider.^{1.6} Gutsche^{1.7} and Böhmer^{1.8} to be calix[4]resorcinarenes or resorcinol-derived calix[4]arenes.^{1.7, 1.8}

1.2 Resorcinarene Synthesis and Stereochemistry

The preparation of resorcinarenes involves an acid-catalyzed condensation reaction between resorcinol and an aldehyde. The reactants are usually heated and allowed to reflux in a mixture of ethanol and concentrated hydrochloric acid for several hours.

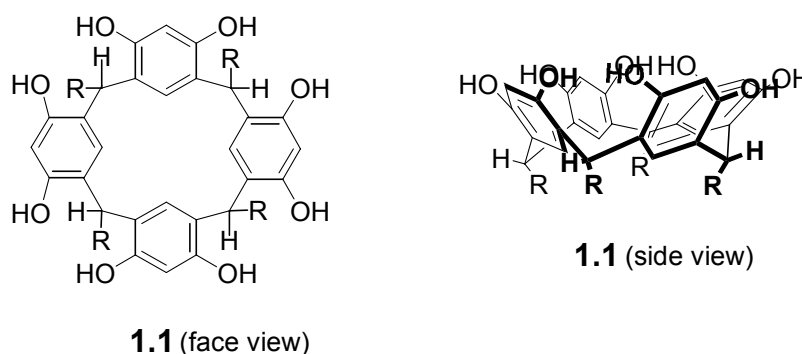


Figure 1.1. Proposed cyclic tetramer by Niederl and Vogel.

However, the optimal reaction conditions vary depending on the aldehyde. In some cases the addition of water is necessary to isolate the product but, the resorcinarene product generally crystallizes from the reaction mixture.^{1.9} These synthetic schemes typically require an unsubstituted resorcinol. In addition, substituted resorcinols such as 2-methylresorcinol and pyrogallol have afforded some amounts of product which were isolated.

In contrast, a resorcinarene product is not generated when resorcinol derivatives contain an electron withdrawing group at the 2-position or when the phenolic hydroxyl groups are partially alkylated.^{1.10} In contrast, a broad range of aliphatic and aromatic aldehydes can be employed to yield product; with the exception of sterically hindered aldehydes such as 2,4,6-trimethylbenzaldehyde or aliphatic aldehydes with functionalities too close to the reaction center (e.g. glucose).^{1.10a, 1.11}

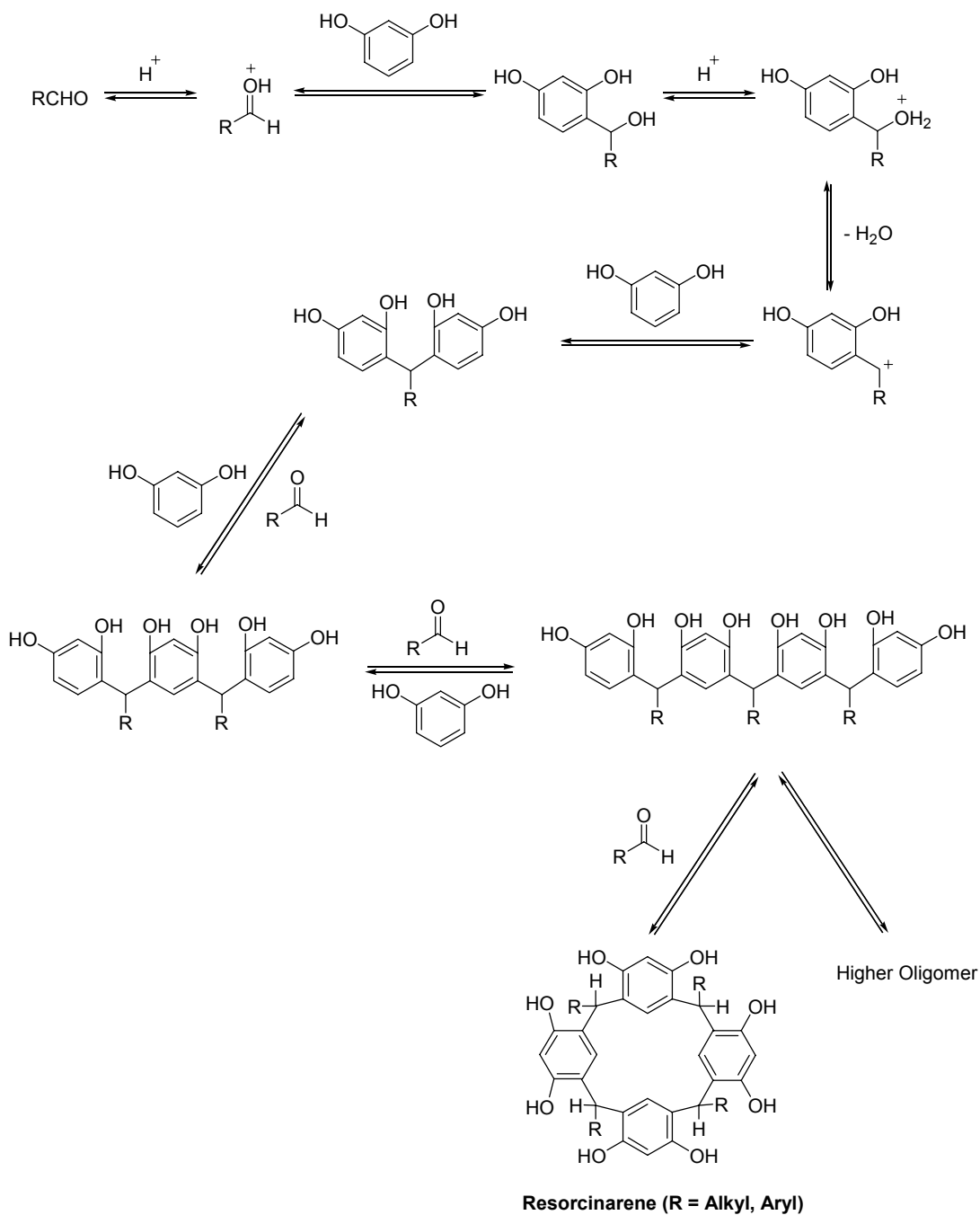


Figure 1.2. Proposed mechanism for the acid-catalyzed synthesis of resorcinarenes.

The mechanism for the formation of resorcinarenes is now well understood.^{1,11} The first step involves the protonation of the aldehyde (Figure 1.2), followed by an electrophilic addition to resorcinol. The resulting –OH is protonated forming H₂O which

is lost. This species undergoes an electrophilic addition with a second resorcinol to form a dimer.

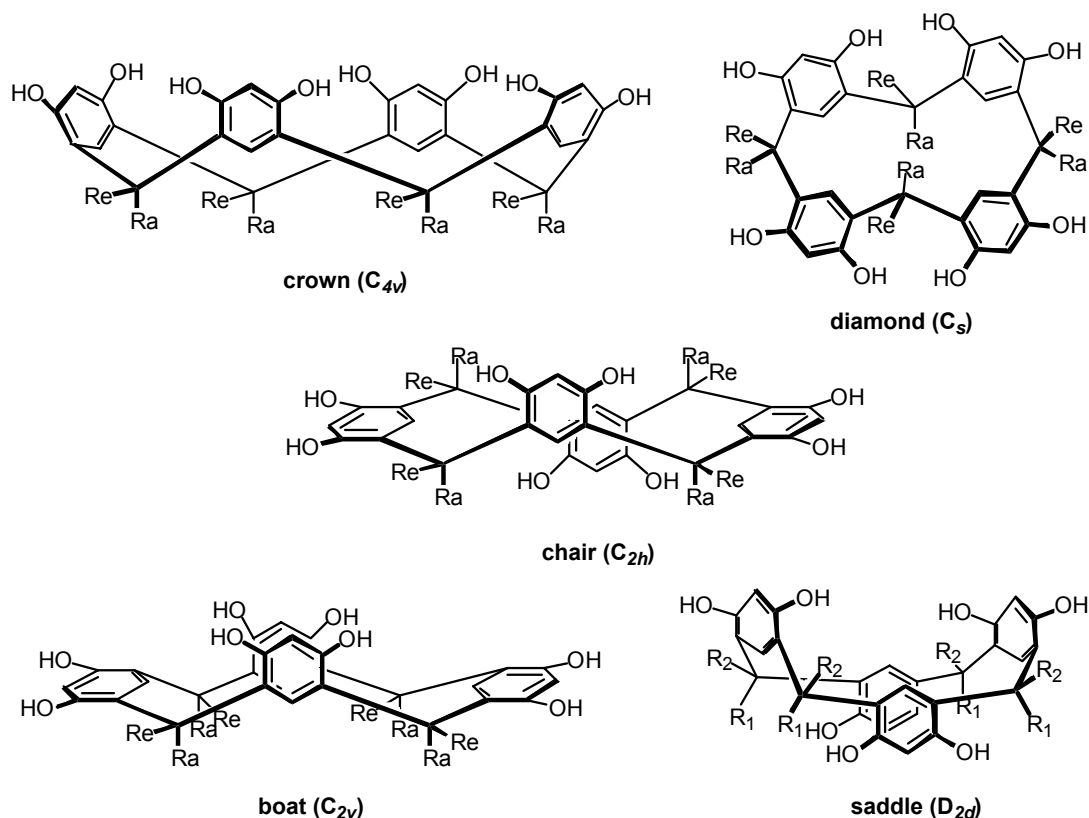


Figure 1.3. Macrocyclic ring stereoisomers.^{1,2a}

This process is repeated forming trimers, tetramers and higher order polymers. At the tetramer stage, cyclization usually occurs to form a resorcinarene. This cyclization is due to their conformation, which is bent in order to form stronger hydrogen bonds between phenolic groups on adjacent resorcinol units.

In theory, resorcinarenes can exist in several isomeric forms, which are governed by three factors. The first is the conformation of the macrocyclic ring, where five symmetrical conformations (Figure 1.3) are possible: the crown (C_{4v}), boat (C_{2v}), chair (C_{2h}), diamond (C_s) and saddle (D_{2d}). The boat, chair and diamond isomers have a

diastereomeric relationship. The two most common isomeric forms are the boat and chair. The boat conformation is often reported as being a crown. This is because boat conformers interconvert very rapidly giving a time-averaged crown structure.

The breaking of at least two covalent bonds leads to interconversion. The ratio in which the isomers are formed vary widely depending on reaction conditions. Under homogeneous conditions the thermodynamic stability of the different isomers

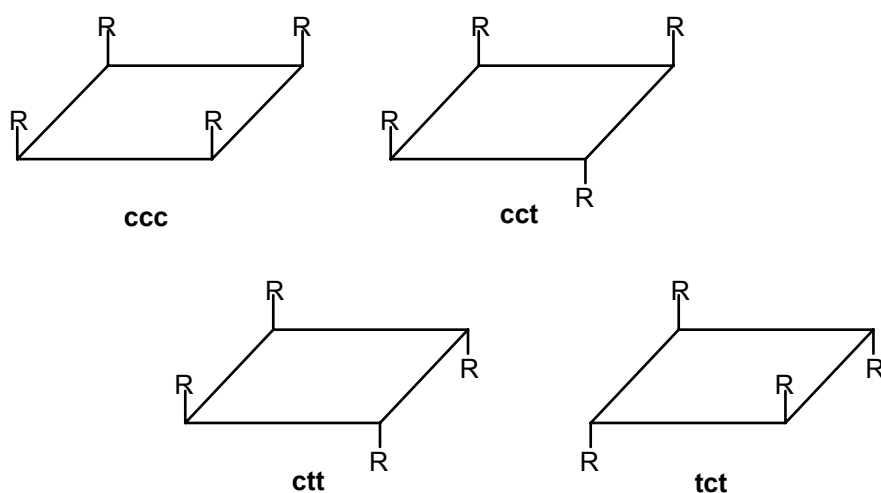


Figure 1.4. Relative configuration of substituents at the methylene bridge.^{1,2}

usually determines their ratio due to the fact that these reactions are reversible under acidic conditions. Under heterogeneous conditions, product solubility is the major determining factor, with the least soluble isomer usually being the main product. The relative configuration of the substituents at the methylene bridges is the second factor (Figure 1.4). The third factor is the individual configuration of the substituents which can be either axial or equatorial. Only four resorcinarenes have been observed experimentally despite the large number of isomers possible.

1.3 Binding of Polar Organic Molecules

Resorcinarenes can bind polar organic molecules due to the presence of eight phenolic hydroxyl groups on the upper rim. Aoyama and co-workers were the first to study the complexation of polar organic molecules using resorcinarenes.^{1.12} The boat isomers were employed, as is common with most resorcinarene research. A large portion of their research focused on the binding of cyclohexanediols. They found that *cis*-1,4-cyclohexanediol was the most strongly bound of the isomers studied.^{1.13} This observation can be attributed to pre-organization of the resorcinarene where one of the two related hydroxyl group is axial and the other is equatorial in the *cis* isomer. This allows for more favorable interactions between the hydroxyl groups. In addition, binding interactions of the *cis* isomers were eight times stronger than the corresponding *trans* isomers. Compared to their cyclic counterparts, open chain diols exhibited much weaker binding interactions.^{1.14}

Resorcinarenes can also bind carbohydrates. The 1,4-*cis* selectivity is also observed with sugar complexation.^{1.15} Upon complexation with resorcinarenes D-ribose, which is insoluble in CCl₄, has revealed some degree of solubility. NMR studies have shown that it is bound exclusively in the α -pyranose form which is the only isomer possessing the 1,4-*cis* orientation. Additional extraction experiments have shown that a 3,4-*cis* arrangement strongly enhances binding. The C-2 hydroxyl does not play a major role in the binding process. The major factor governing complexation is hydrogen bonding; however, a significant contribution is also made by CH- π interactions between the aliphatic moiety of the guest and the aromatic rings of the resorcinarenes.^{1.16}

Resorcinarenes also possess the ability to bind to amino and carboxylic acids.^{1.17} Amino acid complexations have only been investigated in water and those with polar side groups exhibit only insufficient binding. Amino acids containing aliphatic and aromatic side groups showed much better interactions due to greater CH- π interactions. Resorcinarenes hydrogen-bond with dicarboxylic acids in chloroform. The number of carbon spacers between the carboxylic moieties determines the strength of the binding interactions. For example, glutaric acid, which has a three-carbon spacer, is bound more than one hundred times stronger than pimelic acid, which has a five-carbon spacer.^{1.17b}

1.4 Background on Boronic Acid Binding to Saccharides

Boron containing compounds have played a significant role in organic synthesis for many years.^{1.18} Great interest has been shown towards the synthesis of aromatic boronic acid compounds that can serve as receptors for molecules such as saccharides.^{1.19} The first synthesis of phenylboronic acid was performed in 1880 by Michaelis and Becker.^{1.20} Kuivila and co-workers published the first binding studies of boronic acids to diols in 1954. They discovered that boronic acids solubilized saccharides and polyols, and they proposed the formation of a cyclic ester product.^{1.21} Their result corresponded with the well known ability of borates to form complexes with polyhydroxyl compounds.^{1.22} Later in 1959, Lorand and Edwards published the first quantitative interactions between boronic acids and saccharides.^{1.23}

In the reaction of boronic acids with diols, a covalent bond is formed with 1,2- or 1,3-diols for the formation of a five or six membered cyclic ester in both basic and nonaqueous media (Figure 1.5). Saccharides containing rigid, *cis* diols are able to form more stable cyclic esters than acyclic diol. Due to the isomerization

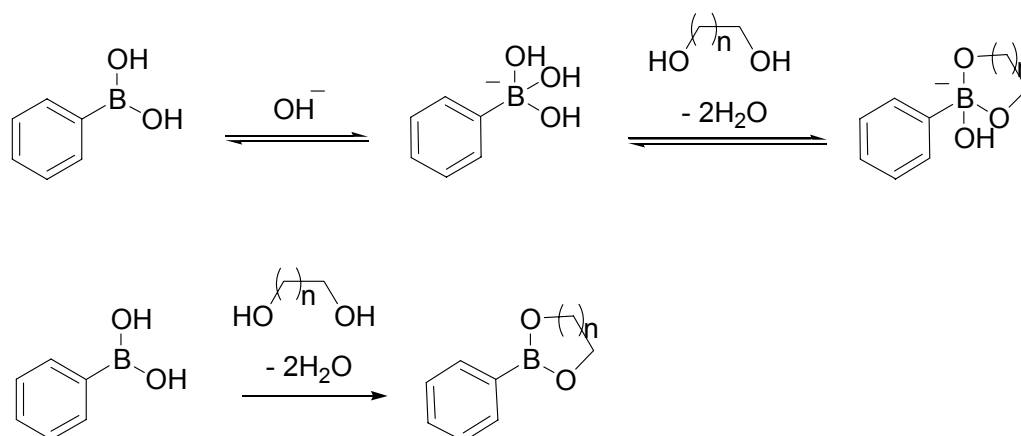


Figure 1.5 Formation of boronate esters with phenylboronic acid. Top: Reaction with aqueous base. Bottom: Reaction in aprotic media.

of the saccharide from the pyranose to furanose forms, the structure of the cyclic ester formed with saccharides is often complex. Based on their studies, Lorand and Edwards found that phenylboronic acid had the following binding affinity for saccharides: D-fructose > D-galactose > D-mannose > D-glucose.^{1,23}

1.5 Significance of Boronic Acid Binding to Saccharides

The recognition of biologically important compounds by synthetic receptors is of great interest. Since saccharides play a significant role in the metabolic pathway of living organisms, the ability to detect the presence and concentration of biologically important sugars such as glucose, fructose, and galactose in aqueous solution is of interest to medicine and industry. Notable interest is placed towards the recognition of D-glucose, because the breakdown of glucose transport in humans has been linked to diseases such as renal glycosuria,^{1,24, 1,25} cystic fibrosis,^{1,26} diabetes^{1,27, 1,28} and cancer.^{1,29} There are a variety of industrial applications ranging from monitoring the process of fermentation to the determination of the enantiomeric purity of synthetic drugs. The current enzymatic

detection methods for saccharides can be limited in specificity. In addition, enzymatic sugar sensors are very unstable under harsh conditions. Thus, the development of a stable boronic acid derived receptor could lead to saccharide receptors that are sugar specific.

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CHAPTER 2

ELUCIDATION OF THE MECHANISM OF DYE FORMATION OF RESORCINOL CONDENSATION PRODUCTS

2.1 Introduction

This was a collaborative project with other members of my research group. My personal contribution to this project involved:

- 1.1.1 Synthesis and isolation of substructures of the resorcinarene macrocycle
- 1.1.2 Providing initial evidence of retro-condensation and oxidation

2.2 Background

Resorcinarenes are unique three-dimensional cyclic aromatic tetramers. The colorimetric properties of resorcinarene solutions had not been studied since Bayer's initial investigation. In 1872, in an effort to develop new dyes,^{2.1, 2.2} he reported the acid-catalyzed condensation of resorcinol and benzaldehyde,^{2.3} which resulted in the first resorcinarenes.^{2.4} He observed a crystalline product and a reddish resin. The product mixture turned purple upon the addition of base. Nierdl and Vogel established the cyclic tetrameric crystalline product in 1940.^{2.5a} The exact structure of these macrocyclic molecules was not confirmed however, until Erdtman and coworkers performed a single X-ray analysis in 1968, almost 100 years after the initial synthesis of resorcinarenes.^{2.6, 2.7} Four different resorcinarene isomers have been found experimentally since that time.^{2.8} The impact of resorcinarenes in the disciplines of molecular recognition, supramolecular chemistry, and materials science has been the subject of extensive study and review.^{2.9}

Boronic acids as functional groups have recently achieved prominence in palladium-mediated coupling reactions,^{2,10} carbohydrate recognition, and sensing studies.^{2,11} Boronic acids readily form strong, reversible covalent bonds to diols to form boronate esters which are utilized as efficient asymmetric homologation substrates^{2,12} and catalysts.^{2,13} Resorcinarenes are the first compounds shown to bind sugars in apolar media. Since boronic acids are known to be the basis of carbohydrate

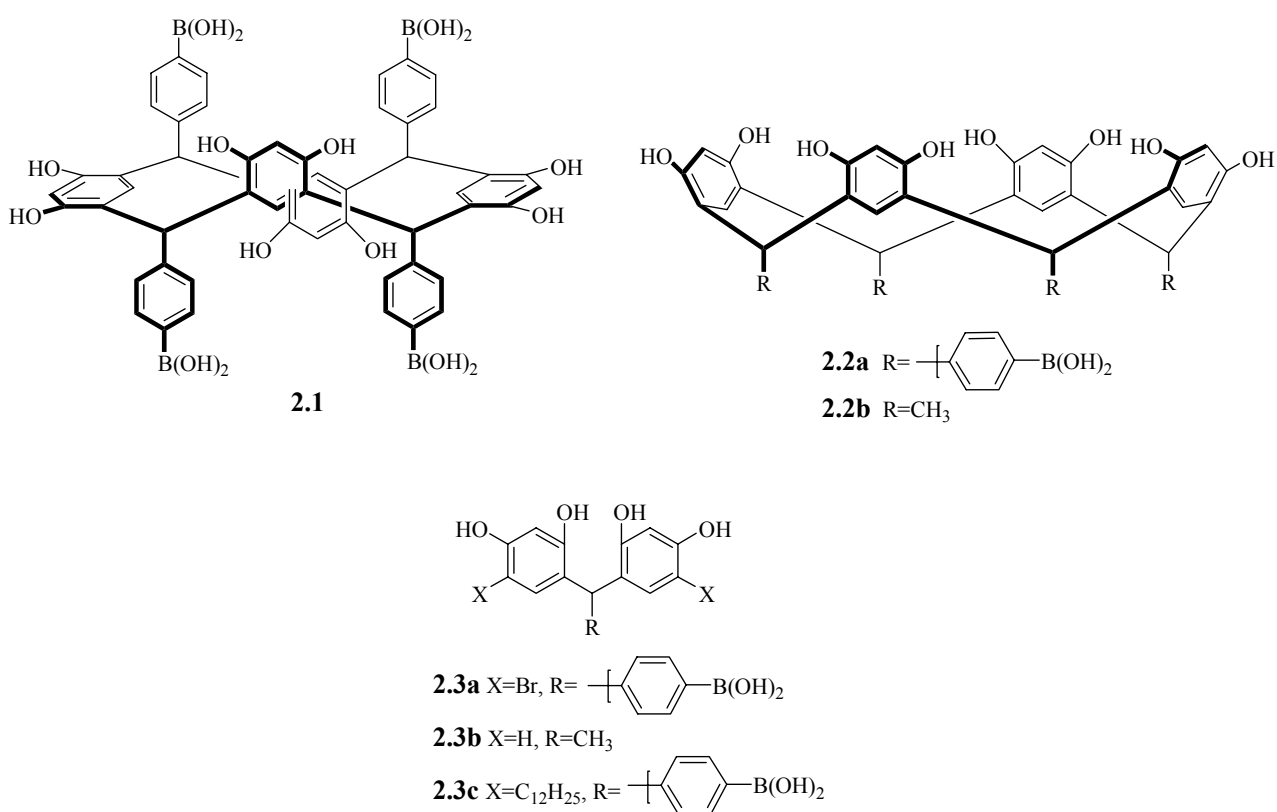


Figure 2.1 Solutions containing resorcinarenes and related condensation products exhibit significant color changes in the presence of sugars.

affinity chromatography;^{2,13} the incorporation of arylboronic acid moieties into resorcinarenes framework might afford powerful sugar receptors. Thus Lewis and Davis synthesized **2.1** and **2.2a** (Figure 2.1) and investigated their properties in the presence of sugars.^{2,14}

Sugars exhibit great similarity in structure and are transparent in the visible region (they lack chromophores or fluorophores), which makes analysis difficult. However, a resorcinol color test was reported by Seliwanoff in 1887, which was followed by other resorcinol-derived methods.^{2.15} Numerous other related reducing sugar assays, typically require toxic reagents, tedious and often harsh procedures.^{2.16} Significant progress was made in the 1990's towards the improved selective and mild detection of monosaccharides via relatively strong solution color changes evident by visual inspection. Recent advances were due to the pioneering efforts of Shinkai and coworkers, where they studied primarily aniline-functionalized azo dyes containing appended arylboronic acids.^{2.17} Presented herein is evidence that xanthenes form and behave as the active chromophores in resorcinarene solutions.

2.3 The Formation and Structure of the Chromophore in Resorcinarene Solutions

The synthesis of compounds **2.1** and **2.2a** has previously been reported.^{2.14} When separating the two stereoisomers by fractional crystallization white crystalline solids were afforded. X-ray quality crystals of the half-methyl tetraboronate ester of **2.1** via recrystallization from a 9:1 MeOH:EtOH solution was obtained by Davis. The isomer possessed an interesting solid-state architecture, which was characterized as an infinite, antiparallel, two-dimensional network of macrocycles, each of which exhibited twelve intermolecular hydrogen bonds.^{2.18}

It was noted that upon allowing a colorless DMSO solution of the crystallized resorcinarene macrocycle (5.2 mM) to stand for several hours or upon heating at 90 °C for 1 min, a pinkish purple color change was observed. This color change was evident by

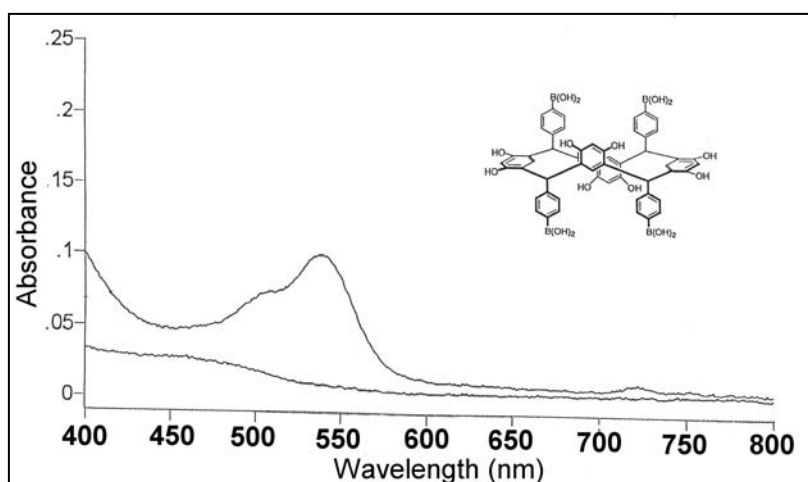


Figure 2.2 Spectral changes of resorcinarene macrocycle upon standing for several hours or upon heating at 90 °C for 1 min.

the increase in absorbance maxima at 535 nm and a less intense λ_{max} at 500 nm (Figure 2.2).^{2,19} Heating the macrocycle **2.1** in aqueous DMSO and in the presence of a variety of sugars resulted in eleven different solution colors (Figure 2.3).^{2,19} The sugars included

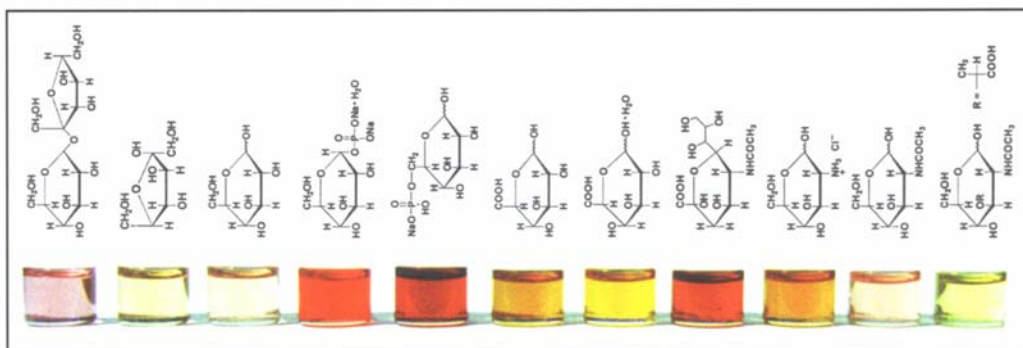


Figure 2.3 Solution colors of macrocycle in the presence of different sugars.

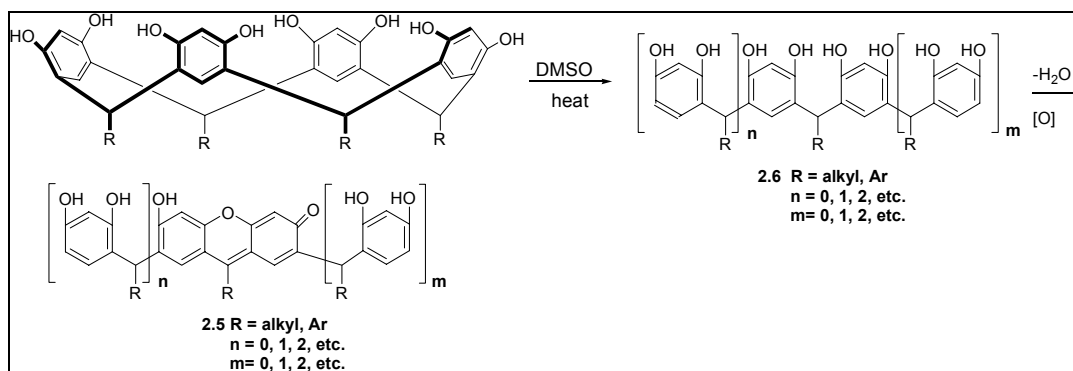
structurally related carbohydrates, glucose phosphates, carboxylic acids, and amino sugars. The color changes were rapid, quantifiable, and reproducible. As a result of these studies we were prompted to determine the origin of the color changes in the

resorcinarene solutions. The color changes over time, when heated, and in the presence of different sugars were the main focus of this investigation.

Initial attempts at understanding the origin of the solution color changes involved; heating solutions of **2.1** in the absence of visible light or oxygen. Color intensities that were less intense, as apparent by both visual inspection and UV-vis spectroscopy were observed.^{2.19} For instance, heating a solution of **2.1** (5.2 mM in DMSO) in the absence of oxygen led to a 61% decrease in absorbance at 536 nm. This was evidence that light and oxygen promote color formation.

Furthermore, the solution remained colorless^{2.20} after acylating the phenolic hydroxyls of **2.1** and heating a DMSO solution of the resultant octaacetate to reflux. The phenolic hydroxyls therefore also play a key role in chromophore formation. As a result it was suggested that the chromophore formation arises via oxidation of a resorcinol moiety to a quinone.^{2.19, 2.20} Further investigation into the chromophore formations performed by heating solutions of resorcinol or benzenboronic acid separately or as an equimolar mixture using the same conditions and concentrations, resulted in only faint solution color by visual inspection.^{2.19} This result showed that a methine-bridged resorcinol/aldehyde condensation framework is needed for effective chromophore formation and optical sugar detection.

The macrocycle possesses a similar structural relationship to xanthenes, thus it was proposed that a portion of the macrocycle can undergo dehydration and oxidation to give a xanthene moiety. Methine-bridged condensation product resorcinarene substructures, were noted as reaction intermediates in standard xanthene dye syntheses (e.g., the transformation of **2.5** to **2.6**, $n = m = 0$, Scheme 2.1).^{2.22}



Scheme 2.1 Dehydration and oxidation of macrocycle fragment (methine-bridged resorcinol oligomers) leading to a xanthene moiety.

Xanthenes are some of the oldest known synthetic dyes. Examples include fluorescein, rhodamine B, **2.4a** and **2.4b** and many more (Figure 2.4). It is known that the colorimetric properties of xanthenes are a function of the ionization state of the C-6 moiety.^{2,21} They typically exhibit two absorbance maxima in the visible region, at 530 nm and a less intense λ_{max} at 500 nm.^{2,21}

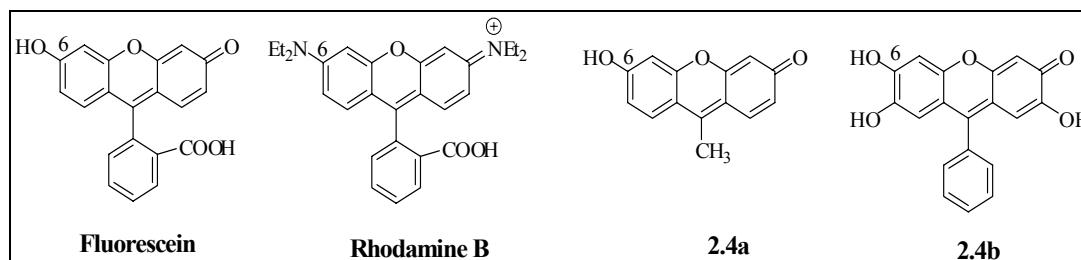


Figure 2.4 Xanthene dyes including **2.4a** and **2.4b**.

An energy-minimized structure of the oxidized macrocycle, showed that incorporation of a planar xanthene within the macrocycle framework would impart considerable strain (Figure 2.5).^{2,23} Upon formation of the xanthene substructure within **2.2b**, simulations (Sybyl 6.6) showed, that an increase in strain energy of 34.2 kcal/mol would occur. Also prior dehydration studies of the related calixarenes (macrocycles

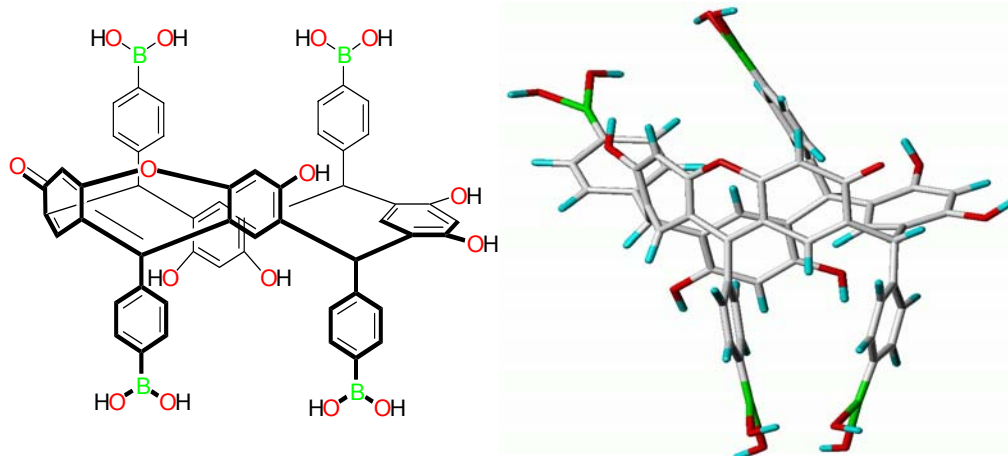
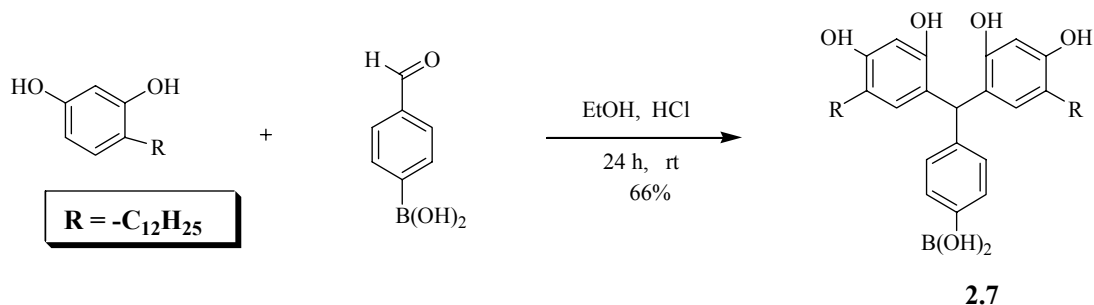


Figure 2.5 Energy-minimized structure (SYBYL[®] 6.6) of a hypothetical macrocyclic xanthene derived from **2.2b**.

formally derived from phenol/formaldehyde condensations) showed that the xanthenes did not form in cyclic tetrameric structures.^{2,24} Thus, it was proposed that in order for xanthenes to form, ring opening to acyclic oligomers must occur.



Scheme 2.2 Synthesis of compound **2.7** (tripod).

An independent study was done using compound **2.7** (tripod) as a substructure of the macrocycle. Compound **2.7** embodies a substructure of the macrocycle **2.2a** (Scheme 2.2). I was able to obtain compound **2.7** in 66% yield by using 4-dodecylresorcinol and 4-formylphenylboronic acid (Appendix A). Figure 2.6 illustrates the relationship

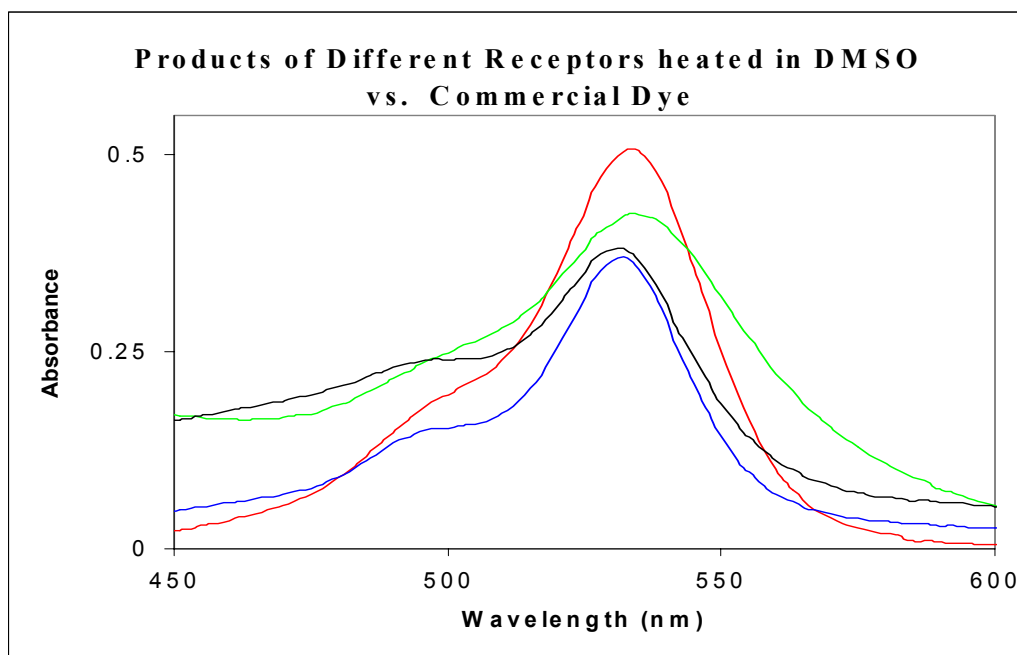
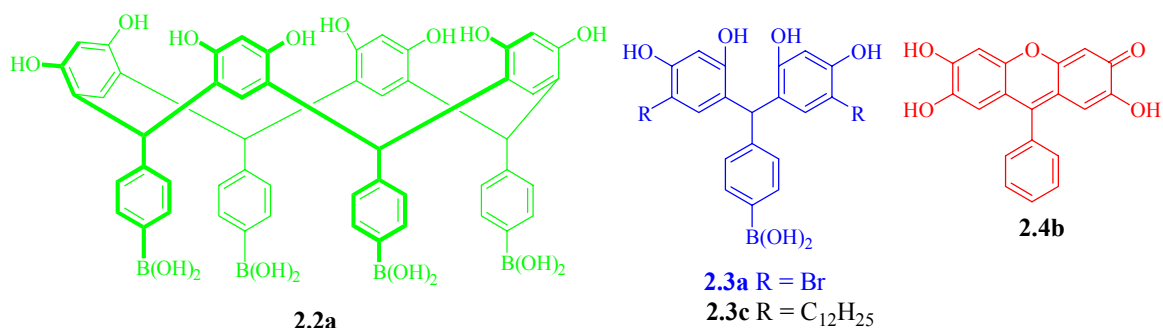
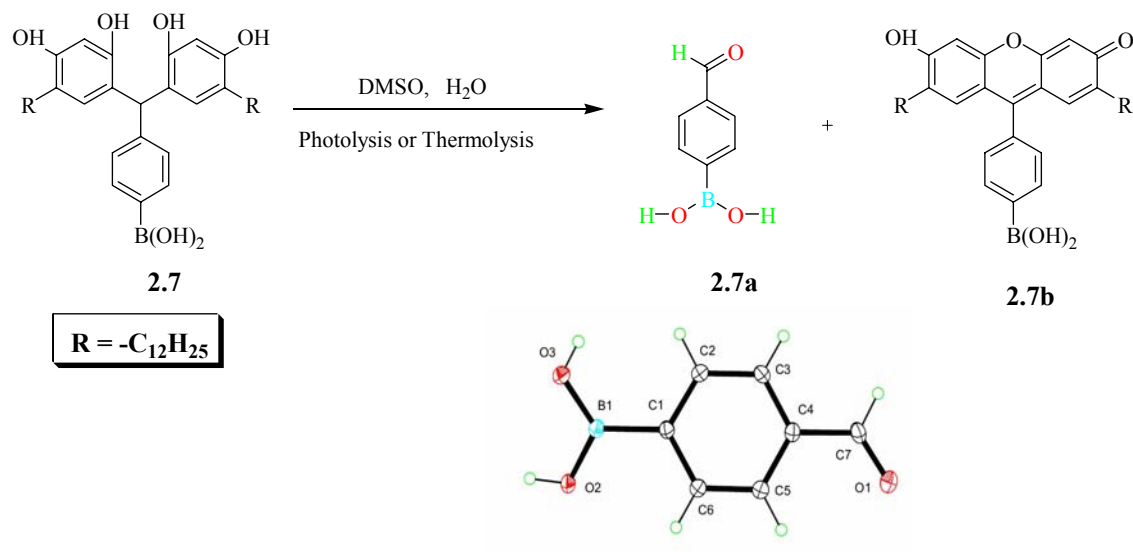


Figure 2.6 **2.2a** (1.0mg), **2.3a** (1.0mg), and **2.3c** (1.0mg) each in 0.9 mL DMSO were heated to a gentle reflux over two minutes and cooled to room temperature before 0.1 mL H₂O was added to each solution. A solution of **2.4b** (5.0×10^{-6} M) was prepared at rt in 9:1 DMSO:H₂O.



between the products of the macrocycle **2.2a**, the brominated and dodecyl tripod when heated in DMSO overlaid with a commercially available xanthene. The overlaid UV-vis spectra shows a similar λ_{max} at about 535 nm accompanied by a less intense one at about 500 nm. This striking resemblance was strong evidence that we were oxidizing and dehydrating our compounds to form xanthenes.



Scheme 2.3 Crystal structure of 4-formylphenylboronic acid **2.7a** and structure of compound **2.7b**.

The synthesis of a xanthene directly from the dodecyle tripod was attempted in the presence of heat and/or light (Scheme 2.3). This resulted in crystals of 4-formylphenylboronic acid (**2.7a**, Appendix B).^{2.25} By means of this, I was able to provide initial and conclusive evidence that under our conditions fragmentation and reversible condensation was occurring.^{2.30} Compound **2.7b**, (Appendix B) the target compound, was produced in traces as evident by both ¹H-NMR and MALDI MS (Figure 2.7).

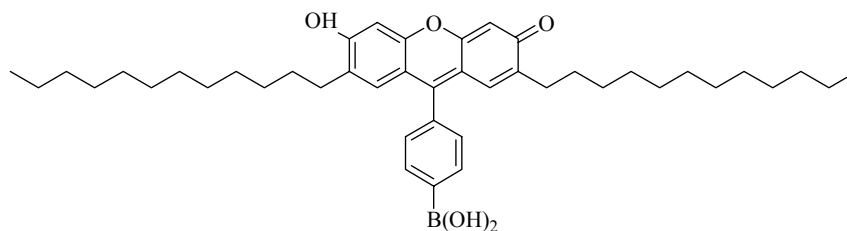
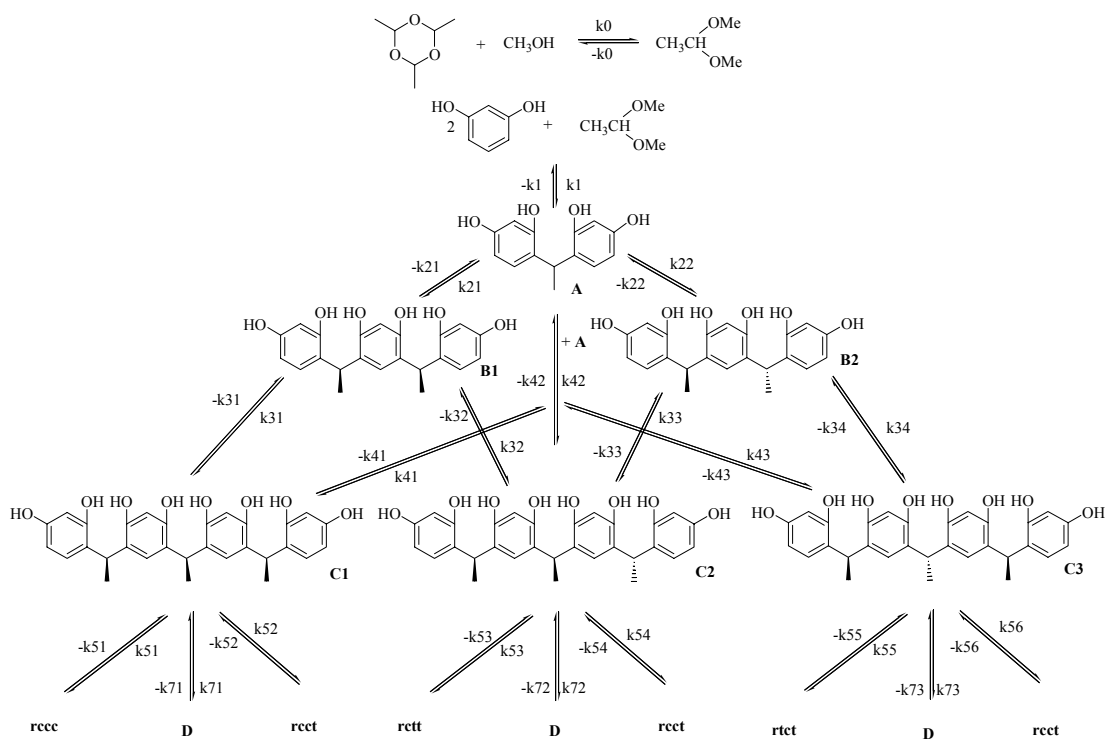


Figure 2.7 Structure of compound **2.7b**.

It is known that condensation reactions producing resorcinarene are reversible under acidic conditions.^{2,4} A report by Weinelt and Schneider^{2,30} showed a detailed study of the genesis of resorcinarene from resorcinol and paraldehyde under acidic conditions.



Scheme 2.4 Reaction of paraldehyde and resorcinol showing the reversible formation of a variety of intermediates in acidic media including acyclic oligomers and resorcinarenes (compound **2.3b** is labeled **A**).

They found that **2.2b** and its macrocyclic stereoisomers interconverted via the intermediate of acyclic oligomers. Their studies include the rapid quenching of the condensation reaction between resorcinol and paraldehyde in MeOH in the presence of anhydrous HCl (Scheme 2.4).

Compound **2.3b** (r.t. =18 min) was isolated from the reaction mixture (resorcinol and acetaldehyde) by preparative reverse-phase HPLC using a gradient H₂O:MeOH 1:1

to 100% MeOH in 20 min (Figure 2.8). The opening of a resorcinarene ring has only been previously shown to occur upon the addition of strong acid, thus, the hypothesis of acyclic oligomer formation in aqueous or neat DMSO solutions without added acid warrants further analysis.

It was noted that ^1H and ^{13}C NMR spectra of DMSO- d_6 solutions of **2.1** (5.2 mM), heated at 90 °C for 3 min exhibited no readily observable change in chemical shifts or peak area integrals compared to fresh, colorless samples.^{2.19} Xanthenes are strongly absorbing materials and so they need be only produced in trace (ca. 0.5% conversion) amounts to afford solution colors under our conditions.

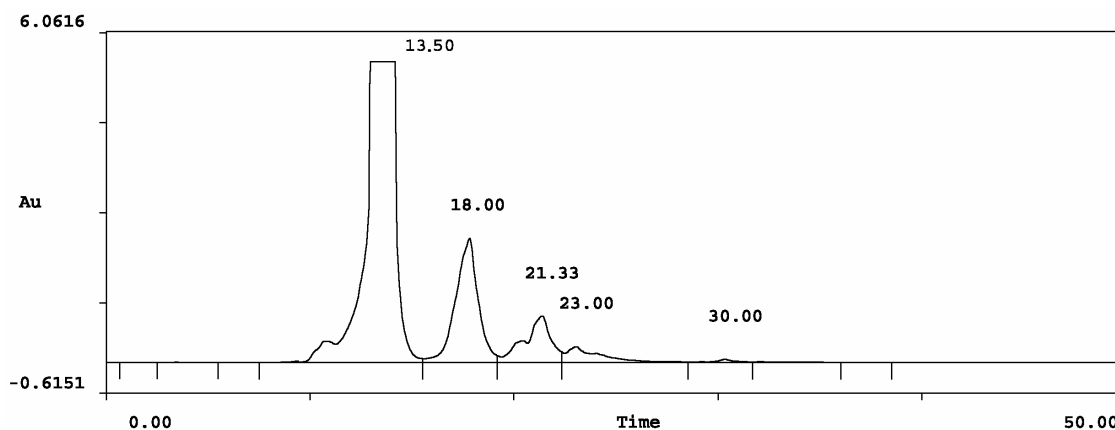


Figure 2.8 Chromatogram of a reaction of resorcinol (r.t. =13.5 min) and acetaldehyde quenched after 10 min according to the procedure reported by Weinelt and Schneider^{2.27} showing the formation of **2.3b** (r.t. =18 min).

2.4 Evidence for Acid Formation in DMSO Solutions

The formation of numerous new products representing a 74 % conversion of **2.2b** to products based on relative peak areas was unveiled. This occurred when a DMSO (10 mL) solution of freshly recrystallized **2.2b** (100 mg, 18.4 mM) was heated at 120 °C for 8h and then followed by analysis via reversed-phase HPLC.^{2.26} It is known that acid production from DMSO is promoted by the presence of O₂ and peroxides.^{2.27} In addition,

certain oxidations in DMSO have been attributed to the *in situ* formation of acid.^{2.27b} Free radical scavengers has been used to inhibit acid formation observed during DMSO decomposition.^{2.27c} Under the same thermolysis conditions as noted above, but in the presence of free radical scavengers (either BHT or PTZ, 10 mol %), less than 28 % conversion to products was observed by HPLC analysis.

Evidence concerning strong acid formation under our conditions was presented describing the first X-ray crystal structure of trimethyl sulfonium methane sulfonate

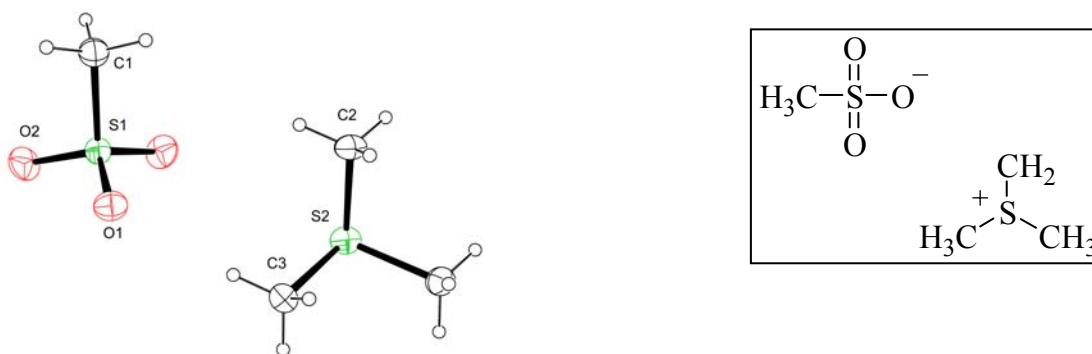


Figure 2.9 X-ray crystal structure of $(\text{CH}_3)_3\text{S}^+\text{CH}_3\text{SO}_3^-$.

$(\text{CH}_3)_3\text{S}^+\text{CH}_3\text{SO}_3^-$, Figure 2.9).^{2.28} This compound was obtained from a thermolysis reaction of **2.2b** in DMSO. It is known that $(\text{CH}_3)_3\text{S}^+\text{CH}_3\text{SO}_3^-$ forms, along with $\text{CH}_3\text{SO}_3\text{H}$, $\text{CH}_3\text{SO}_2\text{H}$ and CH_3SOH (and other products) via the radical and acid promoted decomposition of DMSO.^{2.29} This result confirm that strong acids are formed during the thermolysis of DMSO in the presence of O_2 .

2.5 Macrocycle Bond Breaking and Oxidation of the Acyclic Products

Compound **2.8** (Figure 2.10), is a rarely observed resorcinarene diamond stereoisomer, which was isolated in 2.3% yield from the thermolysis of **2.2b** in DMSO,

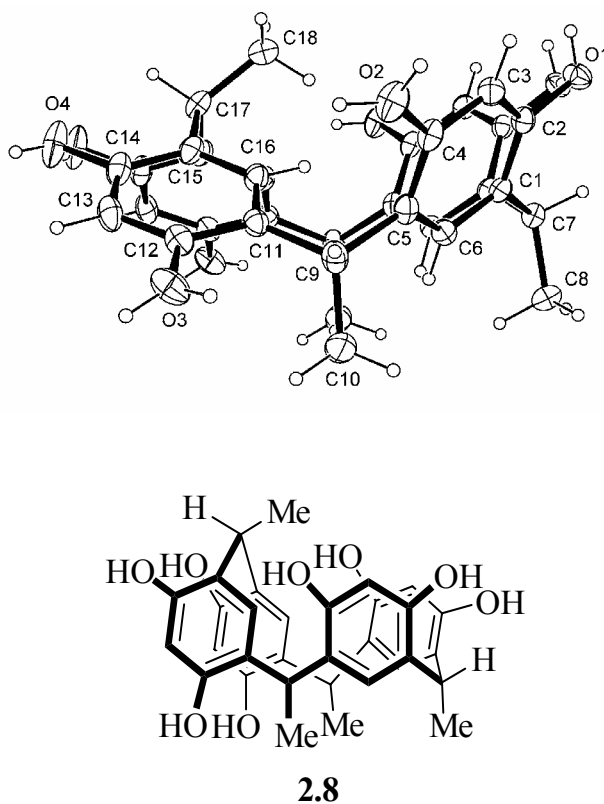


Figure 2.10 Compound **2.8** and ORTEP.

via flash column chromatography.^{2.26} The structure of **2.8** was previously assigned (as the octabutyrate derivative) via NMR evidence during the acid-catalyzed condensation/isomerization studies of Schneider.^{2.30} Notably, stereoisomer **2.8** can only arise from **2.2b** via bond breakage and reformation.^{2.30} If **2.8** were a conformer of **2.2b**, the methyl group (C18), would reside outside, rather than above the plane of the macrocycle cavity.

Acyclic products were seen during the thermolysis of **2.2b**.^{2.26} A key product **2.3b** (also labeled as **A** in Scheme 2.2) was isolated from a broad HPLC fraction eluting from 16-19 min (Figure 2.11). Figure 2.12 depicts two ¹H-NMR spectra; the lower ¹H-NMR (**A**) illustrates pure, independently synthesized **2.3b**, which was isolated from an HPLC column eluting from 16-19 min. The upper ¹H-NMR (**B**) illustrates a HPLC isolated product mixture, which contained **2.3b**, also eluted from 16-19 min.

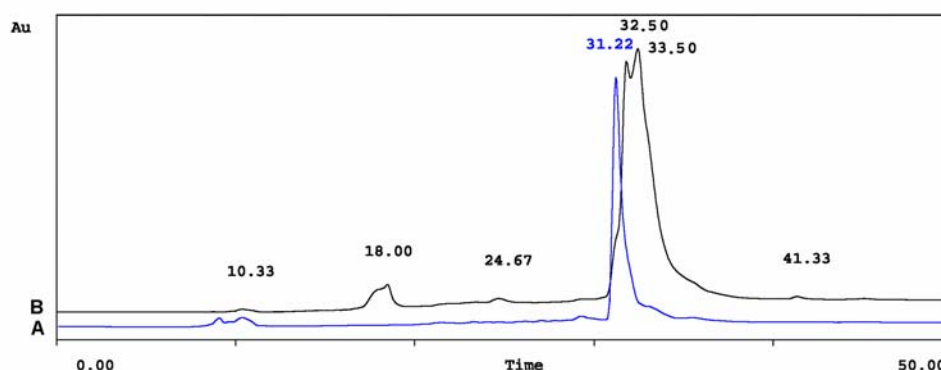


Figure 2.11 (A) Chromatogram of **2.2b** (Control); (B) Chromatogram of the thermolysis products of **2.2b** showing also the formation of **2.3b**.

The ¹H-NMR spectrum of the isolate shows several peaks including each of the resonances associated with **2.3b**^{2.27} [(CH₃OD) δ 1.46 (d, ³J = 7.3 Hz), 4.53 (q, ³J = 7.3 Hz), 6.18-6.22 (m), 6.89 (d, ³J = 8.0 Hz)]. Overlay of the ¹H-NMR spectra of the HPLC isolate with a sample of independently synthesized and isolated **2.3b** confirms the assignment. Additionally, the MALDI MS of the HPLC fraction contains a peak at 245.59 amu (246.26 amu calcd). The production of these compounds (**2.7a**, **2.3b** and **2.8**) under our conditions constitutes an important link between our investigation and the prior acid-catalyzed macrocycle genesis mechanism studies.^{2.30}

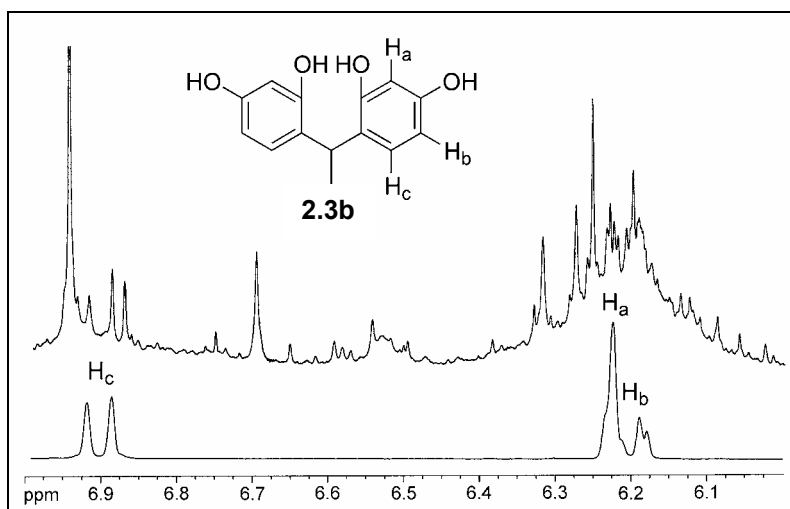


Figure 2.12 Top: expansion of a ^1H NMR spectrum of semi purified thermolysis reaction products of **2.2b** showing the formation of **2.3b**. Bottom: expansion of a ^1H NMR spectrum of pure **2.3b**.

Evidence of higher order oligomer production involving thermolysis of **2.2b** in DMSO was observed. At least five sets of doublets appear between 0.72 and 1.53 ppm in the ^1H NMR of each of two flash column fractions (TLC R_f = 0.54 and 0.63, 9:1 CH_2Cl_2 : CH_3OH , δ 1.53, 1.08, 1.01, 0.97, 0.83, 0.72 ppm, and δ 1.29, 1.15, 1.00, 0.89, 0.84 ppm, CH_3OD , respectively). In addition, the MALDI mass spectrum (anthracene matrix) of other fractions (R_f = 0.29 and 0.44) exhibit peaks for higher homologues of **2.3b** (entries 1 and 2, Table 1.1). MALDI MS evidence also suggests the formation of xanthene materials not previously reported in previous fragmentation and equilibration studies of **2.2b** (Table 2.1, entries 3-6).^{2.31, 2.32}

Several products were formed by heating an air-saturated solution of **2.3b** (0.880 g, 3.576 mmol) dissolved in DMSO (78 mL) at 100 °C for 28 h. This was done in an effort to study oxidation products. The very complex ^1H NMR of the crude mixture reveals the presence of resorcinol as the predominant (90 %) product and a minor conversion to 2,4-dihydroxy-acetophenone **2.9** (ratio of integrals of resorcinol triplet 6.94

ppm to **2.9** doublet at 7.76 ppm is 153:1, CH₃OD) and very small traces of xanthene **2.4a** (d, 7.65 ppm).

Table 2.1 MALDI MS evidence for the formation of acyclic oxidized and unoxidized products from the thermolysis of **2.2b**.

Entry	Structure	TLC R _F	(<i>m/z</i>) calcd	(<i>m/z</i>) obsd
1	2.4 , R=Me, m=1, n=0	0.29	382.41	381.89
2	2.4 , R=Me, m=3, n=2	0.44	926.36	926.28
3	2.6a	0.44	226.23	225.61
4	2.5 , R=Me, m+n=4	0.26	906.01	906.33
5	2.5 , R=Me, m+n=3	0.84	770.79	770.82
6	2.5 R=Me, n=1, m=0	0.79	362.51	361.38

The production of resorcinol and **2.9** (Figure 2.13) gives further evidence that is consistent with the reversible opening and fragmentation of the resorcinarenes in acidic media.^{2,30} Also, in acidic media, the addition of water at the methine carbon of **2.5** (R=Ar,

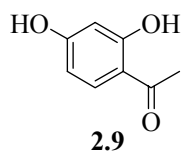


Figure 2.13 2,4-dihydroxyacetophenone (**2.9**) formed upon oxidation of a DMSO solution of **2.3b**.

n=0, m=0) followed by elimination has been described as an intermediate step in the synthesis of xanthenes.^{2,33} By reducing thermolysis time to 2 h better conversion to xanthene **2.4a** from **2.3b** was accomplished. The ¹H NMR spectrum (DMSO-*d*₆) of the crude reaction mixture clearly shows a doublet at 7.65 ppm characteristic of **2.4a** with

improved S/N compared to the 28 h experiment (*vide supra*). Resonances centered at 5.26, 6.49 and 6.60 ppm are also discernable, overlaying with the ^1H NMR of an analytical sample^{2.33} of **2.4a**. Since it is known that oxidation to xanthenes can be promoted by peroxides and acid,^{2.33, 2.34} heating a solution of **2.3b** (50 mg, 0.203 mmol), H_2SO_4 (0.15 mL) and $\text{K}_2\text{S}_2\text{O}_8$ (1.0 mg) in 1.5 mL MeOH at reflux for 2 h produces the most significant conversion (4 % yield) of **2.3b** to **2.4a** observed to date (Figure 2.14).^{2.35}

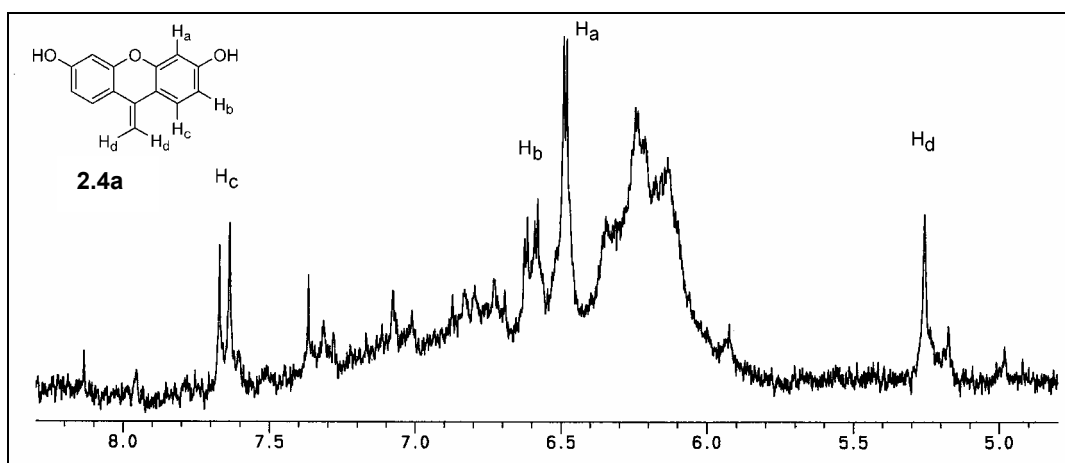


Figure 2.14 ^1H NMR of the products of oxidation of **2.3b** showing the formation of **2.4a** (as its tautomer).

It has now been demonstrated that an oxidative acid catalyzed mechanism is responsible for xanthene formation in solutions containing resorcinarene macrocycles (Scheme 2.1). The O_2 -induced radical decomposition of DMSO leads to strong acid formation *in situ*. The acid catalyzes a reverse condensation reaction to afford acyclic oligomers. The acyclic oligomers undergo oxidation also via the action of acid and peroxide to form xanthenes.

2.6 Interaction of Boronic Acid with Saccharides

The color of xanthene dyes are due to the ionization state of the C-6 hydroxyl functionality.^{2.21} It is known that boronic acid-appended dyes can produce color changes in the presence of saccharides.^{2.36} Importantly, when saccharides form cyclic boronates the Lewis acidity of boron is enhanced.^{2.37} Upon saccharide binding, sp^2 hybridized neutral boron is more readily converted to an sp^3 hybridized anion via the addition of H_2O or HO^- as a fourth ligand (Figure 2.15). This change from a neutral, sp^2 boronic acid to an sp^3 hybridized anionic boronate-saccharide complex has been shown to be the cause of the spectral changes of boronic acid-appended chromophores upon saccharide binding.^{2.36, 2.37b} We thus set out to determine whether the formation of sp^3 -hybridized sugar boronates occurs under our experimental conditions.

The complexation formation between **2.1** and D-fructose was investigated using ^{13}C NMR spectroscopy in a 9:1 $DMSO_{d6}:D_2O$ solvent system to see if the boronate-saccharide complex is formed and what kind of complexes are formed under our conditions. Isotopically labeled D-fructose-2- ^{13}C was employed to study complexation with **2.1**. In the presence of **2.1** (40 mM), D-fructose-2- ^{13}C (1 equiv) in 9:1 $DMSO_{d6}:D_2O$ exhibits several new ^{13}C -2 resonances, which correspond to cyclic sugar boronic esters. The ^{13}C chemical shifts are in agreement with the values obtained by Norrild for the analogous *p*-tolylboronic acid sugar complexes.^{2.38}

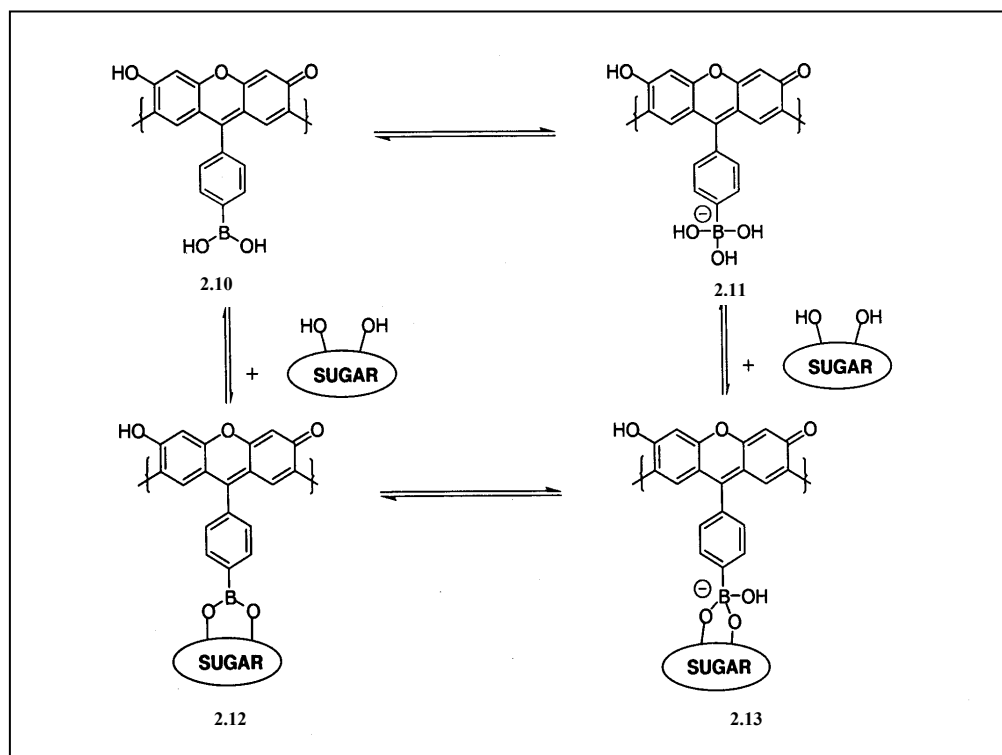


Figure 2.15 Equilibria of boronic acid receptors upon binding to sugar.

Further proof that anionic sugar boronates are forming derives from ^{11}B NMR spectroscopy. The ^{11}B NMR chemical shifts of boronates change as a result of complexation with sugars due to differential electronic shielding of the ^{11}B atom. An upfield shift of the ^{11}B NMR signal accompanies the conversion of sp^2 -hybridized neutral species to sp^3 -hybridized boronate anions.^{2,39} At pH = 6.5, compound **2.1** (10 mM) 1:1 DMSO:H₂O (pH value refers to the buffered aqueous portion before mixing) exhibited a single broad resonance at -19.1 ppm which was assigned to the neutral sp^2 hybridized boronic acid (**2.10**, Figure 2.15). At pH = 11.0, but in the presence of 0.5 equiv D-fructose, a new resonance appeared at -32.9 ppm which intensifies when the amount of D-fructose is increased to 5 equiv. The resonance at -32.9 ppm was thus assigned to D-fructose cyclic boronate anion **2.13**. A solution of **2.1** (20 mM) in DMSO also exhibited a resonance at -32.9 ppm upon D-fructose (3 equiv) addition. The observation of the

resonance at -32.9 ppm corresponding to boronate **2.13** in DMSO is consistent with ^{13}C NMR results.

The formation of the sugar boronate anion allows us to establish a mechanism for the sugar-induced color changes with our receptors. Anionic boronate formation, favored in the presence of sugars, leads to the diminished acidity of the C-6 hydroxyl.

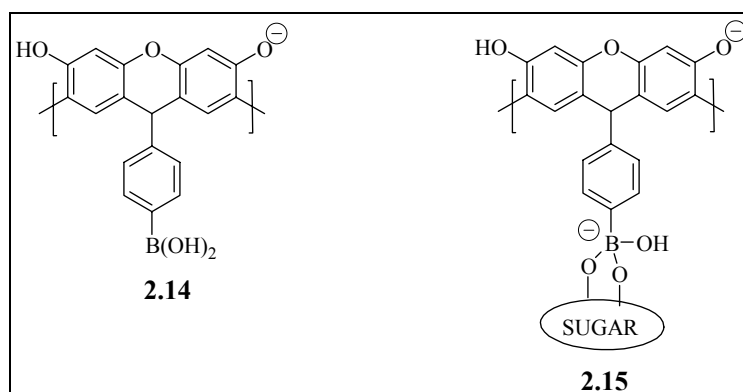


Figure 2.16 Resonance forms of quinone moiety of xanthene.

One way to envision this is via examination of xanthene resonance forms **2.14** and **2.15** (Figure 2.16). Structure **2.15** possesses a more stable cation than **2.14**, making the C-6 hydroxyl of **2.15** relatively less ionizable. Thus, the different binding affinities of the boronic acid for different sugars leads to different color changes observed.

2.7 Conclusion

Strong evidence has been presented that the color changes observed are due to the presence of xanthenes.^{2,3} It has been shown that the colored products existing in solutions of resorcinarene macrocycles can serve as colorimetric indicators. The major findings presented include the determination of the origin and structure of the active chromophore and elucidation of mechanisms associated with the solution color changes induced by saccharides.

Ongoing in our laboratory is the investigation of colorimetric and fluorimetric properties of resorcinarenes, xanthenes, and related chromophoric materials. Our direction is geared towards designing and synthesizing more powerful and selective receptors. We envision xanthenes dyes containing well-positioned boronic acid or related binding moieties should find application as powerful receptors for saccharides and other polar analytes such as carboxylates, and phosphates, and even amino acids.

Resorcinarenes, however, do offer potential advantages compared to functionalized dye materials. One advantage is their ease of synthesis in one step on a 200 g scale.^{2,4d} Given that we have addressed many of the main mechanistic issues associated with the colorimetric sugar detection process, we are now also focusing on the study and optimization of important applied sensing parameters such as detection selectivity, sensitivity and reversibility in aqueous and biological media.

2.8 Experimental

General. Matrix Assisted Laser Desorption Ionization mass spectra were acquired using a Bruker Proflex III MALDI mass spectrometer with either anthracene or dithranol matrices. FT-IR spectra were recorded at room temperature on a Perkin-Elmer 1760X FT-IR spectrophotometer. UV-Visible spectra were recorded at room temperature on a Spectramax Plus (Molecular Devices). Analytical thin-layer chromatography (TLC) was performed using general-purpose silica gel on glass (Scientific Adsorbants). Flash chromatography columns were prepared with silica gel (Scientific Adsorbants, 32-63 μm particle size, 60Å). Analytic and preparative-scale HPLC were performed on a CM4000 multiple solvent delivery system (Milton Roy) and a Spectromonitor 5000 photodiode array detector (LDC Analytical) using a Dynamax 60Å C18 (21.4 mm ID x 25 cm L)

with a flow rate of 5 mL/min and a gradient of 50% water/MeOH to 100% MeOH in 20 min. unless otherwise stated. The following compounds were prepared according to literature methods: **2.1**,^{2.14} **2.2a**,^{2.14} **2.2b**,^{2.5} **2.3a**,^{2.20} **2.3b**,^{2.30} and **2.4a**.^{1.22} All other chemicals were purchased from Sigma or Aldrich and used without further purification. Proton NMR spectra were acquired in either CD₃OD, CH₃OD or DMSO-*d*₆ on a Bruker DPX-250, DPX-400, or AMX-500 spectrometer. All δ values are reported with (CH₃)₄Si at 0.00 ppm or DMSO at 2.45 ppm as references.

X-ray crystallographic data. Intensity data were collected on a Nonius Kappa CCD diffractometer equipped with MoK α radiation and a graphite monochromator. The sample was cooled to 120 K by an Oxford Cryosystems Cryostream chiller. Data collection parameters and crystallographic data are provided in Supporting Information. Absorption and decay effects were negligible. The structure was solved by direct methods, using SIR97³⁰ and refined using SHELXL97.³¹ H atoms were observed in difference maps, but were constrained to be in idealized positions in the refinement. OH hydrogen atoms are all disordered into two sites, all of which were treated as half populated. O-H distances were constrained to be 0.84 Å, but otherwise, these H positions were refined.

Compound 2.7. To a 300 ml three neck round bottom flask, 4-dodecylresorcinol (2.00 g, 7.18 mmol), 4-formylphenylboronic acid (0.538 g, 3.59 mmol), and ethanol (30 ml) were added and stirred until clear. Concentrated HCl (15 ml) was added dropwise to the reaction mixture. The mixture was allowed to stir at room temperature under N₂ for 24 hours. The reaction mixture was neutralized with sodium bicarbonate, and filtered. Ethanol was removed in vacuo. The compound was extracted into ethyl acetate and the

solvent was removed in vacuo. The compound was purified by a solid-liquid extraction using DCM. That provided the filtered compound, (1.64g, 66%) as a lightish brown solid. m.p. >300°C; ^1H NMR (250 MHz, DMSO- d_6) δ 1.31 (m, 46H), 2.25-2.29 (m, 4H), 5.83 (s, 1H), 6.29 (s, 2H), 6.36 (s, 2H), 6.89 (d, J = 7.9 Hz, 2H), 7.61 (d, J = 7.8 Hz, 2H), 7.84 (bs, 2H), 8.74 (s, 2H), 8.78 (s, 2H); ^{13}C NMR (250 MHz, (DMSO- d_6) δ 14.8, 23.0, 29.6, 29.7, 30.0, 30.1, 30.5, 32.2, 41.3, 103.1, 118.1, 121.5, 128.7, 131.8, 134.4, 149.1, 154.1; $\text{uv}\lambda_{\text{max}}$ 465 nm (DMSO/ H_2O); MALDI m/z calcd. for $\text{C}_{43}\text{H}_{65}\text{BO}_6$ 688.8 M^+ , found 688.7 M^+ ; FT IR $\nu_{\text{max}}/\text{cm}^{-1}$ (OH) 3461, (CH₂) 2925, (CH) 2854, (aromatic C=C) 1657, 1521, (COH) 1055, 1027, 1008.

Compound 2.8. Compound **2.7** (0.300 g, 0.448 mmol), 27 mL of DMSO, and 3 mL of water were added to a sealable tube. The mixture was heated to 220 °C for five days. The reaction mixture was then cooled, filtered, and DMSO/ H_2O was removed in vacuo. That provided the compound, (0.210 g, 72%) as a yellowish film-like substance. m.p. >300 °C; ^1H NMR (250 MHz, DMSO- d_6) δ 1.24 (s, 9H), 2.32 (m, 41H), 6.55 (s, 2H), 6.56 (s, 2H), 7.87 (d, J = 8.1 Hz, 2H), 7.99 (d, J = 8.0 Hz, 2H), 8.37 (s, 2H), 10.0 (s, 1H); ^{13}C NMR (250 MHz, (DMSO d_6) δ 13.9, 14.3, 14.7, 22.1, 28.7, 29.0, 31.3, 59.7, 113.5, 115.5, 119.9, 128.3, 129.4, 134.5, 137.1, 151.4, 152.2, 193.5; $\text{uv}\lambda_{\text{max}}$ 535nm MALDI m/z calcd. for $\text{C}_{43}\text{H}_{61}\text{BO}_5$ 668.7 M^+ , found 667.9 M^+ .

Compound 2.7a. Compound **2.7** (0.300 g, 0.448 mmol), 27 mL of DMSO, and 3 mL of water were added to a sealable tube. The mixture was heated to 220 °C for five days. The reaction mixture was then cooled, filtered, and DMSO/ H_2O was removed in vacuo. Compound **2.7a**, (0.200 g, 69%) was acquired as a yellowish film-like substance. X-ray

quality crystal of 4-formylphenylboronic acid were obtained upon slow recrystallization from 98:2 DCM:MeOH.

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CHAPTER 3

SYNTHESIS AND CHARACTERIZATION OF A NEW RHODAMINE-DERIVED BORONIC ACID RECEPTOR FOR THE DETECTION OF SACCHARIDES VIA HPLC POST-COLUMN

3.1 Introduction

This was a collaborative project with other members of my research group. My personal contribution to this project involved:

- 3.1.1 Optimizing the synthesis of the rhodamine boronic acid receptor
- 3.1.2 Developing an HPLC method for isolation of rhodamine boronic acid receptor
- 3.1.2 Providing characterization data

3.2 Background

The structural diversity of carbohydrates has caused great difficulty in analytical detection, hence, their analysis by HPLC is very useful.^{3.1} Carbohydrates generally cannot be detected by absorption in the visible and ultraviolet regions or by fluorescence, because of their lack of chromophores or fluorophores.^{3.2} The detection of specific saccharides could aid in the monitoring of disease.^{3.3} For example, high intake of D-fructose, is associated with several diseases, such as hypertriglyceridaemia, and atherosclerosis.^{3.4} There has been a high demand for efficient, reliable, and inexpensive techniques for carbohydrate detection.^{3.2} In general, the working ranges of some known methods require high pH values, greater than pH 9, in aqueous media. They can be detected by measuring refractivity, but this method is not sensitive enough to detect samples of less than 10 nmol and, in addition, this method can be affected considerably

by changes in column temperature and solvent composition.^{3.2} Due to this, the refractivity detection is usually limited to isocratic chromatography.^{3.2} Ultraviolet detection operated below 210 nm limits solvent choice and requires ultra pure solvents. Mass spectrometry, coupled with chromatographic separations, requires specialized, expensive equipment. Evaporative light scattering detection (ELSD) has attracted great recent attention for the chromatographic detection of carbohydrates; however, molecules with a lower MW range that have the potential to evaporate along with the mobile phase may require advanced detector design. Buffer choice is also limited to only a few salts due to evaporation with the mobile phase. The system also requires relatively high maintenance.^{3.5}

Much effort has been made to develop methods for the colorimetric or fluorometric detection of carbohydrates. Carbohydrates may be derivatized with chromophores or fluorophores prior to separation; however, this procedure can hamper separation by the addition of compounds with inherently similar properties. Thus post-column derivatization systems have attracted great attention in carbohydrate analysis.^{3.1, 3.2, 3.6} Detection systems based on a specific post-column reaction of sugars were the first ones used in the automated liquid chromatography of these compounds. Nevertheless, these detection systems based on the use of strong acid^{3.7} are difficult to handle, required a specially designed acid-resistant reagent delivery and detection system, caused excessive peak broadening and are incompatible with some solvents for separations such as acetonitrile.^{3.1, 3.8} Recently, the development of much milder reactions with fluorogens have been reported.^{3.9}

The reagents currently used in post-column derivatization are typically selective for a family of compounds (for instance, aldoses, ketoses, uronic acids, aminosugars, etc.). The reactions are irreversible. The use of more selective synthetic chromogenic and/or fluorogenic receptors as post-column detection agents could significantly improve the analysis of a component of interest. Furthermore, if binding is via non- or reversible covalent interactions, recovery of expensive or rare biomolecules should be possible.

Presented herein is the synthesis of a new rhodamine-derived boronic acid **3.1** (Figure 3.1), which is used as a post-column derivatization agent in an automated HPLC method for the detection of mono- and oligosaccharides.

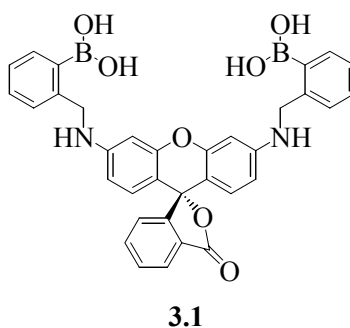


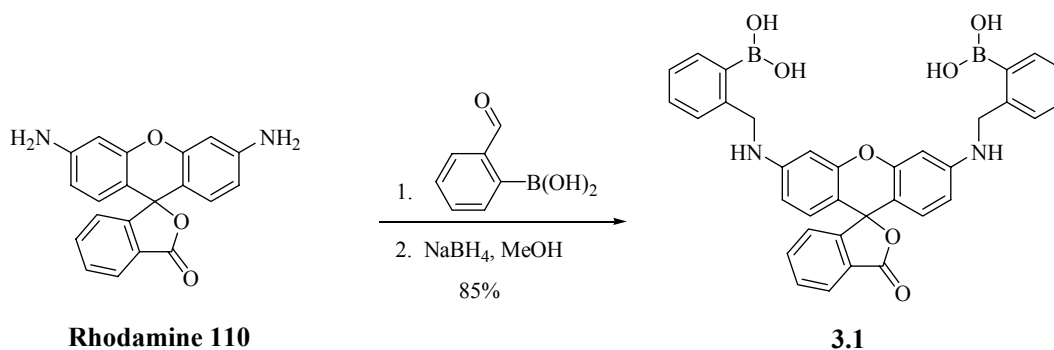
Figure 3.1 Compound 3.1.

3.3 Synthesis and Isolation of Receptor Compound

Boronic acids have been known for over one century since Michaelis and Becker first synthesized phenylboronic acid in 1880.^{3.10} It wasn't until 1959 that Lorand and Edwards published a quantitative evaluation of the interaction between boronic acid and saccharides. They discovered based on formation constants that phenylboronic acid is selective towards fructose over glucose.^{3.11} Phenylboronic acid forms a strong and reversible covalent bonding interaction with saccharide even in aqueous media. Due to this, increasing interest in saccharide recognition by phenylboronic acid has intensified.

Previous saccharide receptors formed hydrogen bonding interactions with saccharides which limits the choice of solvent media.^{3,3} Shinkai and James have both carried out numerous interesting studies utilizing phenylboronic acid towards saccharides.

It has been proposed by Wuff^{3,12} and confirmed by Shinkai^{3,13} that having an intramolecular nitrogen-boron interaction can lower the pseudo pK_a of the boronic acid and therefore allows for strong binding of saccharides at lower pH including neutral pH values. Rhodamines are among one of the oldest known synthetic dyes and show excellent molar absorptivity ($\sim 10^5 \text{ L mol}^{-1} \text{ cm}^{-1}$) in the visible region of the spectrum. These properties allow rhodamines to be used as fluorescent markers for microscopic studies and the detection of specific nucleic acid sequences as photosensitizers and laser dyes. The nitrogen of the amino groups of the rhodamine, influences the absorption, which could also be utilized to promote boron-nitrogen intramolecular interaction. Based on this, compound **3.1** was synthesized (Scheme 3.1).



Scheme 3.1 Synthesis of rhodamine-derived boronic acid receptor.

The synthesis of compound **3.1**^{3,14} was carried out by condensing rhodamine 110 with 2-phenylboronic acid, followed by reduction with NaBH_4 in MeOH. This dye proved typically difficult to isolate and characterize. However, I was able to optimize the

synthesis by implementing a different protocol. I also developed a HPLC method for the isolation and characterization of compound **3.1**. Thus, by preparative scale HPLC, I obtained an analytically pure sample for sensing work and characterization data including MS and ^1H NMR.

3.4 Design of a Post-Column Reactor System

A schematic of the HPLC post-column derivatization system used in our laboratory is shown in Figure 3.2. After injection, the saccharides move into a carbohydrate column to be separated prior to derivatization by way of a delivery pump. Compound **3.1** is delivered from the reagent reservoir via pressurized gas. Both saccharide and receptor meet at the mixing tee. Following this the mixture moves into the reactor where they react, forming chromophoric species. Each of the separated

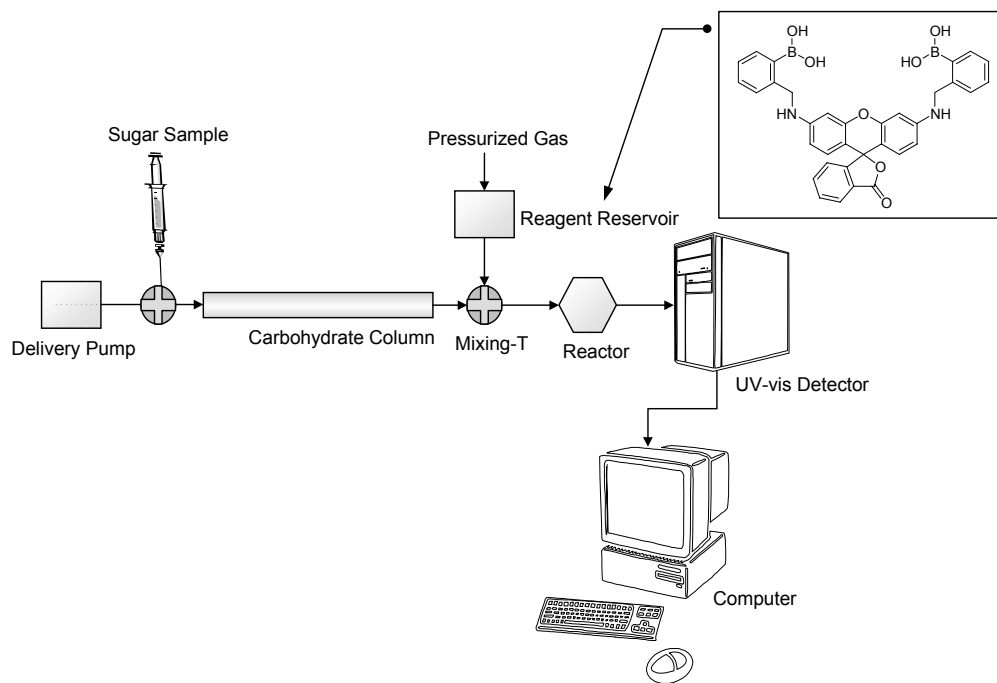


Figure 3.2 Diagram of our post-column chromatographic set-up.

saccharides is converted into detectable derivatives. This is done by the continuous process of mixing the flow of reagent solution followed by reaction for an appropriate length of time at a suitable temperature. The mixed effluent is then passed through the reaction tube. The reaction species formed are then successively led to the detector (commonly used UV-Vis) and finally, the data is outputted onto the computer.

This process is naturally automatic, since separated carbohydrates and reagent are supplied in steady streams and the products formed after reaction in the combined stream are transported to a detector cell.

3.5 Results and Discussion

Compound **3.1** showed selectivity for fructose over glucose in solution. (Figure 3.3). Fructose is an important, common energy source and a sweetener metabolized at a high rate in animals and humans. Thus, proper determination of the level of D-fructose in humans (and animals) requires better methods of analysis. For example, excess glucose

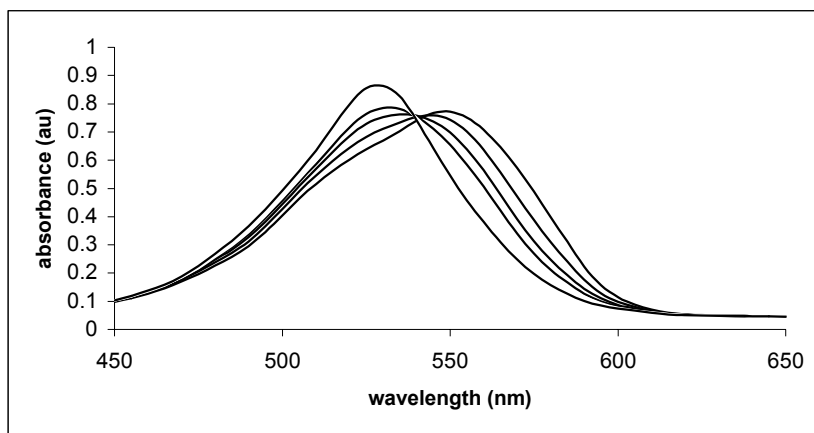


Figure 3.3 RBA = 1.645×10^{-5} M, 0.16 M, pH 9.5 carbonate buffer in a mixture of 1:2 ratio of methanol and H₂O, the final concentration of fructose was 8.33×10^{-4} M.

(100-fold) in plasma impedes the reliable determination of low levels of D-fructose.^{3.15}

However, we can monitor mixtures of D-glucose and D-fructose via automated post-column HPLC detection in the presence of compound **3.1**.^{3.16} As a result, mixtures of D-glucose and D-fructose were injected at different ratios. When a mixture of 20 µg of each sugar with compound **3.1** was injected, D-fructose (LOD: 2.3×10^{-6} g) exhibited a

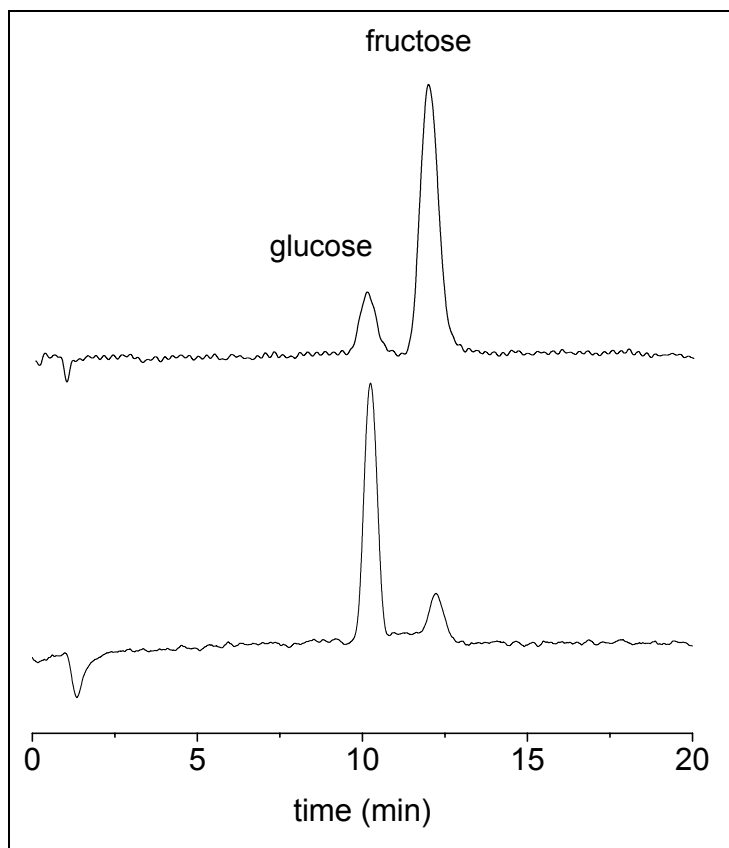


Figure 3.4 Top: chromatogram of a 1:1 mixture of D-fructose (r.t. = 10.0 min) and D-glucose (r.t. = 12.0 min, 20.0 µg). Bottom: chromatogram of a mixture of D-fructose (4.5 µg) in the presence of a 100-fold excess of D-glucose.

higher response compared with D-glucose (LOD: 7.1×10^{-6} g). Also, in the presence of a 100-fold excess of D-glucose a peak can be seen for D-fructose (Figure 3.4). This emphasizes the advantage of this method over other methods.

We are also able to detect oligosaccharides using the HPLC post-column method. Oligosaccharides are much more difficult to detect than monosaccharides. The classical color tests for monosaccharides fail to directly detect oligosaccharides containing more than three residues.^{3.17} Current oligosaccharide colorimetric HPLC detection methods typically require prior complete hydrolysis to monosaccharides or pre-column covalent attachment to a chromophore.^{3.18}

We have developed a method which allows us to generate strong colorimetric responses for larger oligosaccharides. This method is based on our recent report of boronic acid functionalized dyes exhibiting binding constants for the linear maltodextrins series that increases with increasing molecular weight.^{3.19} These findings has been used to employ a new colorimetric HPLC detection method for oligosaccharides. Using similar conditions as used for the monosaccharides mentioned, mixtures of maltotriose and maltohexaose (80 μ g) were monitored via HPLC post-column (Figure 3.5).

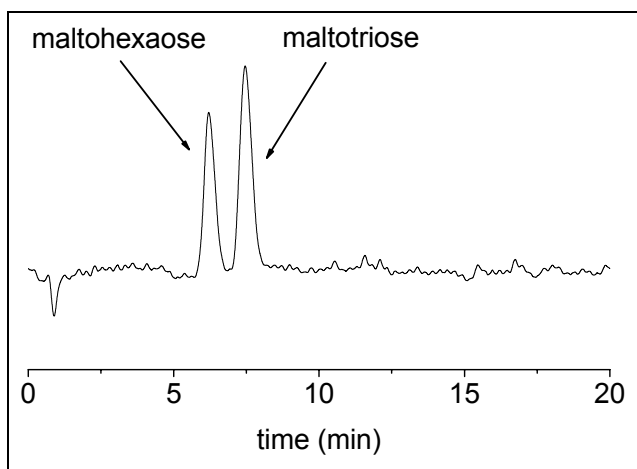


Figure 3.5 Chromatogram of a 1:1 mixture of maltohexaose and maltotriose (80 μ g).

3.6 Conclusion

In conclusion, I have presented the synthesis of a new boronic acid dye **3.1** and confirmed its use as a detection agent for saccharides in an automated post-column HPLC system. The selectivity of **3.1** for fructose can advance fructose monitoring in the presence of a large excess of glucose. The affinity of **3.1** for oligosaccharides allows for colorimetric monitoring upon their chromatographic elution. The synthesis and properties of chromophoric and fluorophoric synthetic receptors are currently being investigated in our laboratory. We are considering to explore the fluorescent properties of **3.1** that may lead to much better limits of detection and to use this compound in biological samples.

3.7 Experimental

General. Matrix Assisted Laser Desorption Ionization mass spectra were acquired using a Bruker Proflex III FAB mass spectrometer with glycerol matrix. UV-Visible spectra were recorded at room temperature on a Spectramax Plus (Molecular Devices). HPLC experiments were performed on a CM4000 multiple solvent delivery system (LDC/Milton Roy) and a SpectroMonitor 3100 UV-vis detector (LDC/Milton Roy) using an Alltech 700CH carbohydrate column (6.5 mm ID x 30 cm L) with a flow rate of 0.5 mL/min at a constant temperature of 85 °C. The column is maintained at constant temperature using a CH-30 column heater (Eppendorf)

The post-column detection system consisted of a Helium Cylinder connected to a Timberline[®] RDR-1 Reagent Delivery/Reaction Module. The RDR-1 unit contains a pressurized reagent reservoir, a mixing tee, and a thermostated reaction block with a Teflon[®] reaction coil (0.02 in I.D. x 1 m L) with a nominal volume of 0.2 mL. The HPLC

column was attached to the RDR-1. The RDR-1 was attached to a SpectroMonitor 3100 UV-vis detector (LDC/Milton Roy). The temperature of the reaction block to 50 °C and absorbance is monitored at 560 nm.

Compound 3.1 Rhodamine 110 (0.1 g, 0.27 mmol) and 2-formylphenylboronic acid (0.082 g, 0.54 mmol) were mixed in absolute EtOH (20 ml) and toluene (3.1 ml). A Dean and Stark trap was fitted to permit the azeotropic removal of water, and the reaction mixture was heated at reflux overnight (18-24 hrs). After cooling, the solvent was removed in vacuo to afford a yellow oil. NaBH₄ (0.041 g, 1.08 mmol, 4 equiv.) was added over 5 min to dry MeOH (25 ml). The reaction was left to stir at room temperature for 2 hr, and poured into ice-water (10 ml) where a small amount of saturated NaHCO₃ was added. The aqueous solution was extracted into CH₂Cl₂ (3 x 50 ml). The solvent was removed in vacuo to afford (0.13g, 81%) of product in the aqueous layer. To obtain an analytical standard, further purification was executed by using HPLC, C₁₈ column (70/30 MeOH/H₂O to 100 MeOH in 30 min), T_R = 33.6 min; ¹H NMR (300 MHz, DMSO-d₆) δ 4.53 (s, 4 H), 6.74-6.86 (m, 4 H), 7.11-7.23 (m, 8 H), 7.58-7.63 (m, 2 H), 8.05 (d, J = 7.2 Hz, 2 H), 8.54 (s, 2 H). ¹³C NMR (500 MHz, DMSO-d₆) δ 22.07, 28.66, 28.95, 46.45, 97.17, 105.85, 114.91, 118.83, 122.48, 124.05, 124.33, 125.24, 126.38, 128.13, 128.83, 129.73, 150.87, 152.33, 154.98, 168.87; uv λ_{max} 545 nm FAB-MS m/z (glycerol matrix) calcd for C₃₄H₂₈B₂N₂O₇ 598.22 M⁺, found 710.1 [M + 2 C₂H₆O₂ - 4 H₂O]⁺.

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- 3.16 The reagent solution was prepared by dissolving **3.1** in 0.05M buffer (pH=10.5, carbonates). The reagent was introduced at a flow rate of 0.5 mL/min and the reactor temperature was kept at 50 °C. The mobile phase is 100 % deionized H₂O. Mixtures of D-glucose and D-fructose were injected at various ratios. We observed the best response for D-fructose (LOD = 2.3 µg) even in a 100-fold excess of D-glucose (LOD = 7.1 µg).

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CHAPTER 4

SYNTHESIS, CHARACTERIZATION AND STUDY OF A NOVEL FLUORESC EIN DERIVED PHOSPHONIC ACID DYE FOR THE DETECTION OF VARIOUS COMPOUNDS VIA METAL COMPLEXATION

4.1 Introduction

This was a collaborative project with another member of my research group. My personal contribution to this project involved:

- 4.1.1 Design and synthesis of a fluorescein diphosphonate (FDP)
- 4.1.2 Developing an HPLC method for isolation and providing characterization data
- 4.1.2 Determining stoichiometry of FDP-metal complex
- 4.1.3 Monitoring various compounds using the FDP-metal complex

4.2 Background

Remarkable effort has been devoted to the design of saccharide receptors.^{4.1} Great effort has been made towards the development of new sensing techniques for visual detection of various bioanalytes. Simple methods for detecting and monitoring saccharides are of vast importance to medical diagnostics and industry. A current challenge in this area is the fabrication of readily accessible, stable artificial receptors that promote fast, sensitive and selective detection.^{4.2} Such materials could lead to improved indicators relative to degradable enzyme-based systems or to those requiring complex and expensive syntheses or instrumentation. The design of artificial receptors that bind strongly and selectively to carbohydrates continues to be a very active area in bioorganic chemistry.^{4.3}

Numerous systems for the optical detection of anions and neutral molecules have been reported.^{4.4} However, selective systems are relatively rare and a wider range of application is needed. Fluorescein based indicators are well known as reagents for determination of inorganic pH, anions, drugs and food additives.^{4.5} The big advantage of fluorescein dyes is that many are soluble in aqueous media and shows great molar absorptivity (ϵ) in the visible region of the spectrum. Also, various fluorescein indicators have long been utilized towards numerous analytical applications.

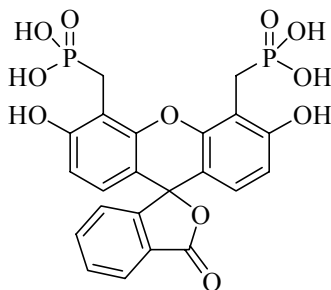
Fluorescein dyes can also be used as signaling units for artificial receptors. Their ability to form complexes with many metals is of great interest. These complexes can be easily monitored by UV-Vis or fluorescent spectroscopy. It is a well known fact, that receptor-metal complexes are widespread in the nature. Numerous membrane receptors in living cells, enzymes, lectins or oxygen transferring proteins contain certain metal cations in their binding sites.

Phosphates and phosphonates represents a group of compounds with interesting binding properties, where the these groups play a vital role as they are known to be strong hydrogen bond donors/acceptors.^{4.6} Several examples of synthetic receptors containing P=O groups have been published in connection with sugar recognition.^{4.6} Receptors containing phosphonate groups have been used for sensing of numerous compounds via the formation of non-covalent complexes.^{4.6, 4.7} They are also known to act as chelators and are able to form strong complexes with different metals.^{4.8}

Based on this we proposed that a fluorescein based phosphonic acid receptor would easily form a binary complex with different metals and can be used for the detection of certain analytes. Presented herein are the binding and complexation studies

between **4.4** with different metals in buffer aqueous solution to reveal binding and signaling in the presence of saccharides, amino acid and other organic and inorganic anions.

4.3 Synthesis of Fluorescein Diphosphonate

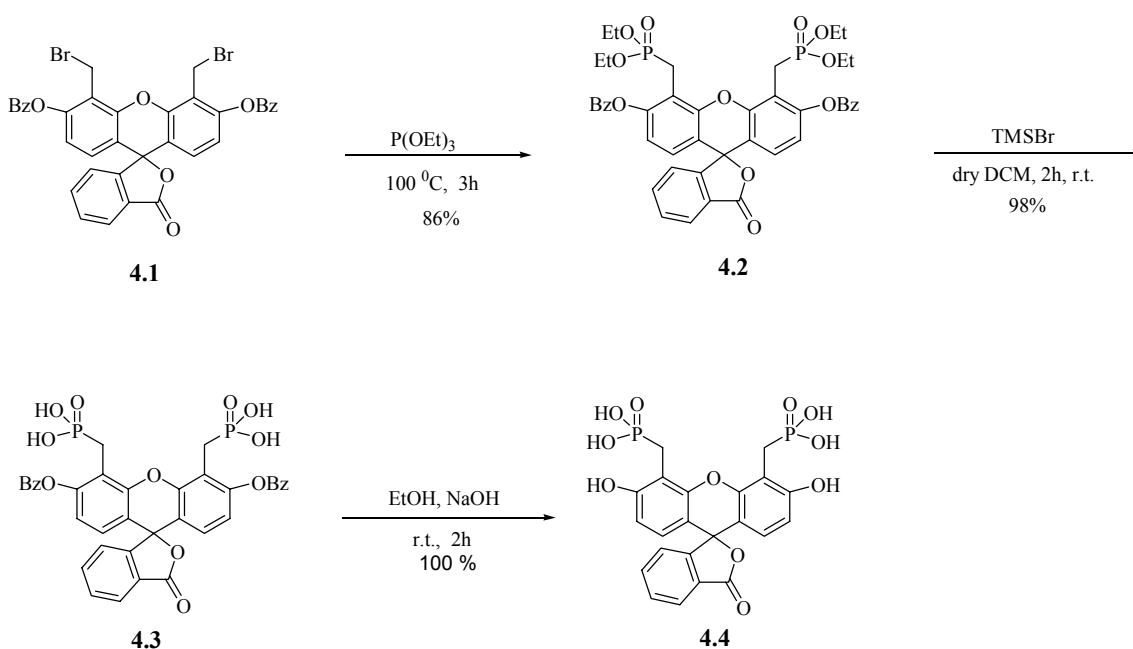


4.4

Figure 4.1 Compound **4.4**.

Based on our previous knowledge with xanthene dyes, I designed and synthesized a fluorescein diphosphonate (FDP, **4.4**) for the purpose of molecular recognition of saccharides. I chose a phosphonate derivative as the basis of the design because such derivatives are known to remain anionic over a wider range of pH than carboxylates ($pK_a \approx 1.8, 6.7$ compared to ≈ 4.8 for carboxylates)^{4,9}

The synthesis of **4.4** begins with an Arbuzov reaction. This involves treatment of 4',5'-bis(bromomethyl)fluorescein dibenzoate, **4.1**^{4,10} with $P(OEt)_3$ to afford compound **4.2** as a yellow oil. An X-ray quality crystal of **4.2** was also obtained (Appendix D). Hydrolysis of compound **4.2** with $TMSBr$ yields compound **4.3**. This is followed by saponification of compound **4.3** to give the desired compound, **4.4**. An analytically pure sample of **4.4** was obtained via HPLC isolation to supply characterization data such as MS, 1H and ^{31}P NMR (Appendix D).



Scheme 4.1 Synthesis of fluorescein-derived phosphonic acid dye.

4.4 Results and Discussion

In our experiments seven metals were examined. These metal ions are known for their ability to form complexes with different biomolecules. All complexation studies were carried out in 0.1M of HEPES buffer pH 7.5. Job plots completed for the different binary dye-metal complexes indicates various stoichiometries. The results showed that the complexes formed are of the 1:1 and 2:1 type ratio (Appendix E). A simple screening assay was carried out utilizing 14 different analytes. This screening involved adding equimolar amount of the analyte to a solution of corresponding **4.4**-metal complex in buffer (final concentration of the dye-metal complex and analyte was 1.1×10^{-4} mol/L). Formation of the chromogenic ternary complexes was monitored by UV-Vis spectroscopy and quantitatively estimated.

Figure 4.2 illustrates graphically the selectivity profile of **4.4**-metal complexes towards the series of the analytes. Control experiments demonstrated only negligible absorbance changes during interaction of free **4.4** with mentioned analytes. We observed a significant selectivity for cyanide anion with **4.4**-Bi(III) and **4.4**-Ni(II) complexes. Complex **4.4**-Zn(II) exhibits an affinity for different types of amino acids, D-glucose and

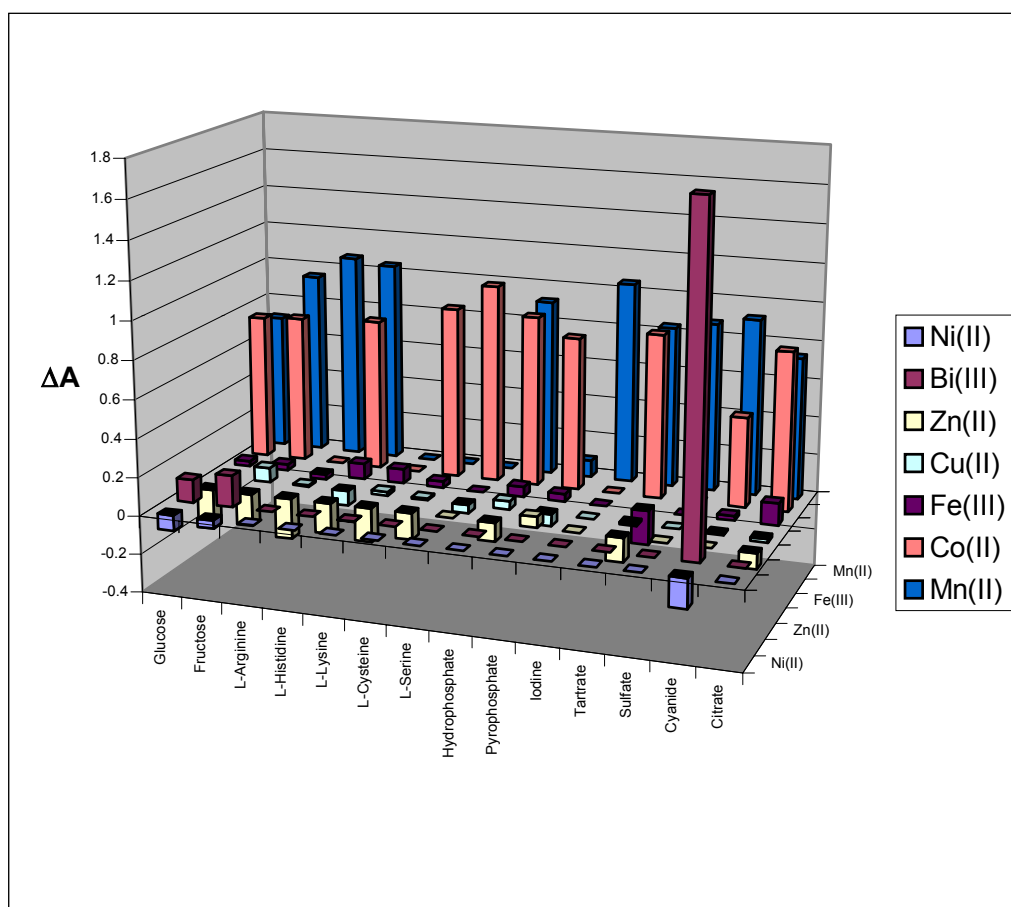


Figure 4.2 UV-Vis absorbance changes ($\lambda = 500$ and 510 nm) of **4.4**-metal complexes in the presence of several saccharides, amino acids and anions.

D-fructose, complex **4.4**-Fe(III) for citrate and tartrate, and complex **4.4**-Cu(II) for D-fructose and L-histidine. Complexes **4.4**-Co(II) and **4.4**-Mn(II) however, demonstrate

significant interaction with just about all the various groups of analytes but, without expressed tendency to bind specifically certain analyte.

The binding of saccharides, anions and amino acids to the **4.4**-metal complex is not yet fully understood. However, it is believed to occur via ternary complex formation in the presence of buffer. We observe a non-boronic acid based selectivity for fructose with certain of these complexes.

4.5 Conclusion

I have synthesized a new fluorescein derived phosphonic acid dye, **4.4** which has potential application for detecting various bioanalytes via metal complexation. The advantages of our detection technique are the simplicity and non-tedious preparation of the complex and experiments with mild buffered conditions. The latter is important due to competition of buffer components with analytes for binding of the receptor. The binding properties of these dye-metal complexes are currently being investigated in our laboratory.

The future direction of this work is guided towards determining the structure of **4.4**-metal complex, which will be done by ^{31}P NMR and related studies. This will enable us to then propose a mechanism by which binding occurs by molecular modeling.

4.6 Experimental

General. Matrix Assisted Laser Desorption Ionization mass spectra were acquired using a Bruker Proflex III MALDI mass spectrometer with either anthracene or dithranol matrices. UV-Visible spectra were recorded at room temperature on a Spectramax Plus (Molecular Devices). Analytical thin-layer chromatography (TLC) was

performed using general-purpose silica gel on glass (Scientific Adsorbants). Flash chromatography columns were prepared with silica gel (Scientific Adsorbants, 32-63 μm particle size, 60Å). Preparative-scale HPLC were performed on a CM4000 multiple solvent delivery system (Milton Roy) and a Spectromonitor 5000 photodiode array detector (LDC Analytical) using a Dynamax 60Å C18 (21.4 mm ID x 25 cm L) with a flow rate of 5 mL/min.

Compound 4.2. To a 50ml round bottom flask 4'5'-bis(bromomethyl)fluorescein dibenzoate, **4.1** (3.00 g, 4.13 mmol) and excess $\text{P}(\text{OEt})_3$ (10 ml, 49.56 mmol) were added. The reaction mixture was allowed to stir for 3 h at 100 °C. A yellow oil was isolated after solvent removal. Flash chromatography on silica gel (98/2 EtOAc/MeOH or 70/30 EtOAc/hexanes) yielded the product (2.99 g, 86%) as a goldish yellow oil. TLC R_f = 0.46 (100 % EtOAc). ^1H NMR (250 MHz, CDCl_3) δ 1.12-1.38 (m, 20 H), 3.73-3.88 (m, 4 H), 6.79 (dd, J = 2.5 Hz, 2.6 Hz 2 H), 7.06 (d, J = 8.7 Hz, 2 H), 7.27 (d, J = 5.0 Hz, 1 H), 7.50 (t, J = 8.2 Hz, 4 H), 7.61-7.72 (m, 4 H), 8.05 (d, J = 7.2 Hz, 1 H), 8.25 (d, J = 8.4 Hz, 4 H); ^{13}C NMR (250 MHz, CDCl_3) δ 16.69, 22.24, 24.49, 30.10, 62.16, 62.55, 62.79, 63.99, 64.09, 82.71, 114.48, 116.80, 119.07, 124.72, 125.68, 126.82, 127.18, 129.33, 130.63, 134.30, 135.72, 150.54, 151.05, 152.91, 164.49, 169.53; ^{31}P NMR (250 MHz, CDCl_3) δ 26.7; MALDI m/z (anthracene matrix) calcd for $\text{C}_{44}\text{H}_{42}\text{O}_{13}\text{P}_2$ 840.74 M^+ , found 841.73 M^+ .

Compound 4.3. To a dried round bottom flask (2.99 g, 3.56 mmol) of compound **4.2**, and 40 ml of anhydrous DCM was added via syringe. The mixture was allowed to stir until **4.2** were completely dissolved. Excess amount of distilled TMSBr (2.82 ml, 21.34 mmol) was then added. The reaction mixture was allowed to stir at room temperature for

2 h. H₂O was then added with continued stirring. The solvent was removed in vacuo after 30 minutes. This provided the product (2.57 g, 98%) as a yellow solid. ¹H NMR (250 MHz, CDCl₃) δ 3.41–3.58 (m, 4 H), 6.67 (d, *J* = 7.95 Hz, 2 H), 6.97 (d, *J* = 8.73 Hz, 2 H), 7.25 (d, *J* = 11.1 Hz, 2 H), 7.47 (t, *J* = 10.9 Hz, 4 H), 7.57–7.67 (m, 2 H), 8.01 (d, *J* = 7.42 Hz, 2 H), 8.34 (d, *J* = 7.20 Hz, 4 H); ¹³C NMR (250 MHz, CDCl₃) δ 7.83, 16.93, 61.73, 82.63, 116.46, 166.55, 120.00, 124.72, 126.27, 126.97, 129.58, 129.80, 130.87, 131.50, 135.02, 137.00, 149.94, 150.83, 150.93, 153.28, 164.63, 169.44; ³¹P NMR (250 MHz, DMSO-*d*₆) δ 17.3; MALDI *m/z* (dithranol matrix) calcd for C₃₆H₂₆O₁₃P₂ 728.53 M⁺, found 729.69 M⁺.

Compound 4.4. **4.3** was suspended in alcoholic sodium hydroxide (5%, 12 ml) and the mixture was kept at room temperature for 2 hr with occasional slow stirring. The reddish solution was poured into water and neutralized with HCl to give an orange solution. The solvent was removed in vacuo to yield quantitatively compound **4.4** (1.20 g) as a reddish solid. To obtain an analytically pure sample, **4.4** was purified by HPLC (50/50 H₂O/CH₃CN to 100% CH₃CN in 40 min, *T_R* = 14.52 min). ¹H NMR (250 MHz, D₂O-*d*) δ 3.30–3.50 (m, 4 H), 6.80 (d, *J* = 9.3 Hz, 2 H), 7.22 (d, *J* = 9.2 Hz, 2 H), 7.38 (d, *J* = 8.5 Hz, 1 H), 7.47–7.52 (m, 1 H), 7.66 (t, *J* = 7.1 Hz, 1 H), 7.86–7.89 (m, 1H); ¹³C NMR (250 MHz, D₂O-*d*) δ 24.74, 26.46, 111.91, 116.12, 120.74, 131.53, 132.55, 133.24, 136.54, 136.78, 137.94, 155.53, 170.47, 175.43, 176.42; ³¹P NMR (250 MHz, D₂O-*d*) δ 21.9; uv λ_{max} = 470 nm (DMSO/H₂O); MALDI *m/z* (NBA matrix) calcd for C₂₂H₁₈O₁₁P₂ 520.32 M⁺, found 520.9 M⁺.

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CHAPTER 5

OPTICAL DETECTION OF L-CYSTEINE AND L-HOMOCYSTEINE VIA A FLUORESC EIN DERIVATIVE

5.1 Introduction

This was a collaborative project with another member of my research group. My personal contribution to this project involved:

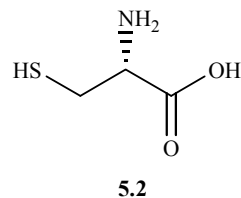
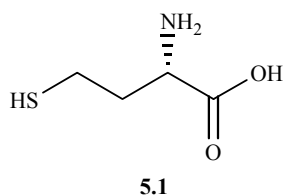
5.1.1 Synthesis of fluorescein derivative

5.1.2 Execution of ^1H NMR experiments

5.2 Background

Naturally occurring thiols exhibit a variety of structures as well as physiological properties that are of great concern to public health. The detection of low molecular weight biological thiols is of great importance for diagnosing and understanding disease states. The amino acid L-homocysteine (Hcy, **5.1**), for instance, has been attracting significant recent attention. It has been shown that elevated amounts of homocysteine in blood plasma is a risk factor associated with serious disorders such as Cardiovascular^{5.1} and Alzheimer's disease.^{5.2} Cysteine (Cys, **5.2**) can be obtained as the final product of the transulfuration pathway through homocysteine metabolism (Figure 5.1). Like homocysteine and other thiols, cysteine can dimerize through disulfide bond formation. Poor water solubility of the disulfide cystine reduces its excretion. It therefore accumulates either in urine, leading to cystinuria^{5.3} or in various organs of the body, forming for example kidney stones.^{5.4} Also low levels of cysteine are associated

with slowed growth, hair depigmentation, edema, lethargy, liver damage, muscle and fat loss, skin lesions and weakness.^{4,5}



General Detection Methods: Due to the risk associated with Hcy, there is a significant need for improved methods for biological thiol detection. There are various detection methods, which mainly include chromatographic separations, immuno- and enzymatic assays, electrochemical, and mass spectrometric technology. Each of these methods contains intrinsic limitations. These restrictions include interference from oxidizable impurities,^{5,6} toxicity, and poor stability. Also some of these methods require long run times,^{5,7} tedious procedures and high operating temperatures.^{5,8} Off course these limitations are due to the fact that thiols are extremely difficult to work with. Firstly, thiols are readily prone to oxidation. They are mostly found in either homodisulfide or mixed disulfide forms. Many have similar structures and are typically colorless and non-fluorescent in the visible region.

Derivatization of Thiols using Chromophores or Fluorophores: Derivatization of thiols are based on chromophores or fluorophores, which can be non-selective and/or unstable.^{5,9} Figure 5.1 contains several representative compounds sold by Molecular Probes for the detection of thiols. They often contain electrophilic alkylating groups for reaction with sufhydril moieties and include iodoacetamides,^{5,10} maleimides,^{5,11} and monobromobimanes (mBrB).^{5,12} Most of these compounds are thiol selective. However, the main drawback is a lack of selectivity among the thiols. In addition, other

interferences are of concern, such as the reaction of iodoacetamides with histidine, tyrosine and methionine.^{5.13}

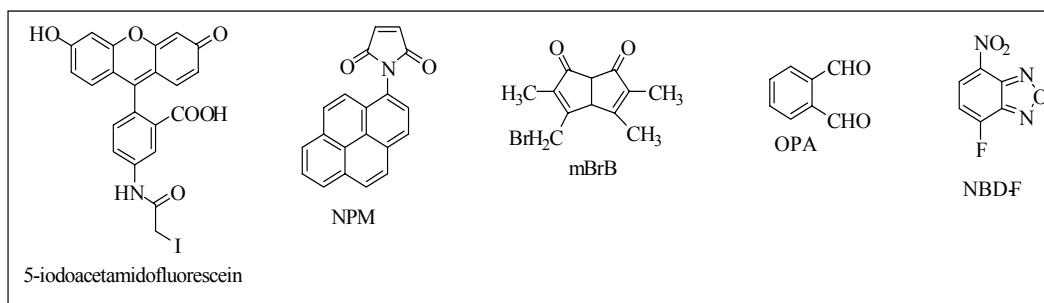


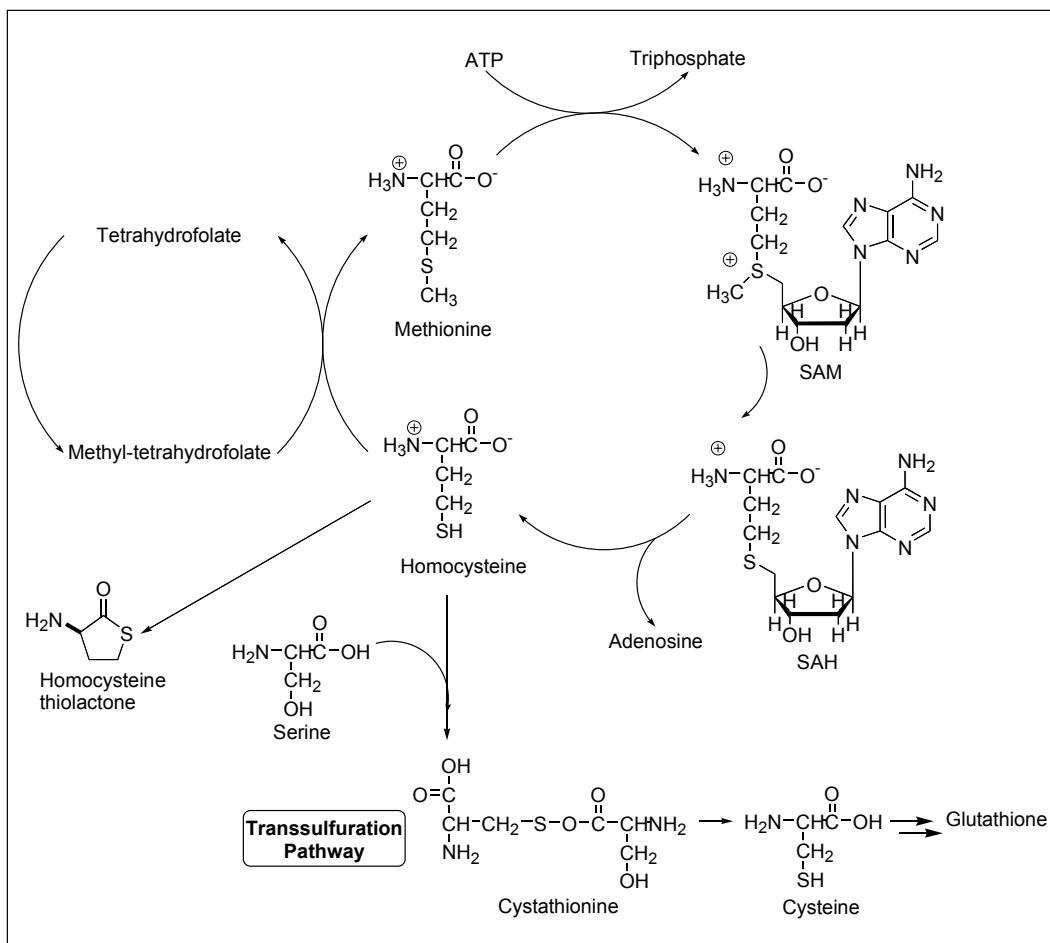
Figure 5.1 Representative known thiol derivatizing agents.

Sample preparation (thiol derivatization) conditions can also lead to problems^{5.14} such as removal of excess derivatization agents from reaction mixture, which can be a time consuming and complex effort. No adduct formation takes place at pH lower than 9.^{5.15} Other concerns include, the tendency of the derivatives to undergo unwanted reactions. For instance, the products of isothiocyanates with biological thiols undergo further reactions with neighboring amines to give thioureas.

Some thiol-chromophores/fluorophores derivatives are sensitive to light and hydrolysis. The OPA-Hcy adduct is stable only in dark.^{5.16} On the other hand, mBrB produces fluorescent hydrolysis products.^{5.17} Some derivatization agents themselves are prone to instability. For example, iodoacetamides are unstable to light^{5.18} and mBrB is known to be photosensitive and unstable in water.^{5.19} Thiol and sulfide quantitation kits are available. The procedure necessitates an enzymatic reaction to release the thiols followed by their determination by Ellman's reagent. However, enzymes are expensive, and fragile which makes them very difficult to work with.

5.2.1 The Importance of Biological Thiols to Public Health

Homocysteine Metabolism: S-adenosylmethionine (SAM), the universal methylating agent, is synthesized from methionine and ATP (Scheme 5.1).^{5,20} SAM, which is used for one carbon metabolism produces S-adenosyl homocysteine (SAH) via methylation. This reaction is followed by the enzymatic hydrolysis of SAH by S-adenosyl homocysteine hydrolyase (SAHH) to afford adenosine and Hcy. At this point, a transsulfuration pathway leading from Hcy to Cys is initiated. The reaction of Hcy with serine via cystathionine- β -synthase (CBS), the vitamin B₆-dependent enzyme, affords



Scheme 5.1 Homocysteine metabolism

cystathionine. Cystathionine is cleaved to form cysteine, which serves as a source of glutathione, sulfate and sulfite.^{5.20}

Cystathionine synthesis is not the only fate of Hcy. Homocysteine can be methylated, released into the extracellular medium or deaminated.^{5.21} Hcy methylation to methionine can be carried out by methionine synthase in a folate dependent manner or via betaine homocysteine methylase.^{5.20}

Hyperhomocysteinemia: Disruption in Hcy metabolism causes the export of Hcy from the cellular to the extracellular medium to become imbalanced. At lower Hcy cellular levels, export rates are elevated. More Hcy is then exported to plasma and urine as a result. Higher Hcy levels in plasma and urine are thus directly related to lower methionine synthase activity and folate or vitamin B₁₂ deficiency. The condition where the concentration of Hcy in plasma exceeds 14 μM ^{5.1, 5.2} is defined as hyperhomocysteinemia. Vitamin or folate therapy has thus been proposed to be useful for hyperhomocysteinemia-related disorders. The physiological effects of hyperhomocysteinemia can be depressed after diagnosis.

Homocysteine in Plasma: After being released into plasma, Hcy is found in several forms. The sum of all these forms is the plasma total homocysteine level. Approximately 99% of Hcy is bound via disulfide linkages to proteins, other Hcy molecules or thiols in plasma. Monomeric Hcy is only ca. 1% of total Hcy content of plasma.^{5.22}

Oxidation to disulfides in plasma is coupled to O₂ reduction, leading to oxidative stress. Reactive oxygen species (ROS) levels can be diminished by peroxidases.

Unfortunately, hyperhomocysteinemia appears to inhibit the expression of peroxidases.^{5.20}

Nitric oxide (NO) released by endothelial cells can react with Hcy to furnish S-nitrosohomocysteine (SNOHO), which is a strong antiplatelet and vasodilator agent. The consequence of nitrosylation is the repression of peroxide production and therefore inhibition of ROS formation.^{5.23} Hcy cannot be effectively deactivated by this mechanism, when present at hyperhomocysteinemic levels.

Hcy is believed to lower NO availability upon nitrosylation.^{5.22} This is due to low-density lipoprotein oxidized by ROS suppresses endothelial nitric oxide synthase expression.^{5.24} NO is a neurotransmitter and involved in muscle relaxation^{5.25} and so, lowered NO availability should be listed among the physiological results of hyperhomocysteinemia. More importantly, Hcy impairs endothelial cell function in the absence of NO. Although the mechanism is not perfectly understood, it is believed that the direct action of homocysteine on endothelial cells could either involve enhanced oxidative stress or result from a direct effect of the oxidation products of homocysteine.

The impairment of endothelial cells by hyperhomocysteinemia is believed to be an origin of cardiovascular diseases. It is believed that Hcy switches their phenotype from anticoagulant to procoagulant. It has been reported that high homocysteine levels were detected in up to 20% of people suffering from heart disease.^{5.23}

Since blood vessels carry oxygen to the brain and heart brain damage could be caused by oxidative stress generated by hyperhomocysteinemia, and, in turn, Alzheimer's disease. Increased risks of birth defects, and^{5.26-5.30} renal failure^{5.31} are other diseases also related to hyperhomocysteinemia. According to recent studies, the over expression of

glutathione peroxidases is encountered in Alzheimer patients, linking the disease to oxidative stress in the brain. Additionally, elevated levels of plasma homocysteine have been detected under the same conditions. Further evidence for the role of oxidative stress is that antioxidant supplement delays the Alzheimer's-related complications.

Glutathione: In addition to disulfide formation, pollutants, UV radiation and other sources such as mitochondria oxidative phosphorylation can cause oxidative stress by generating ROS such as superoxide, hydrogen peroxide (H_2O_2), hydroxyl radical ($\text{OH}\cdot$) and peroxynitrite (ONOO^-). Under oxidative stress conditions, macromolecular lipids, nucleic acids, and proteins can be oxidized. Cells are more readily protected against this threat by native antioxidant molecules and enzymes^{5.32, 5.33} thus avoiding oxidative stress.

Glutathione is the most abundant intracellular non-protein thiol compound. Glutathione dependent peroxidases couple its disulfide-forming reactions with the reduction of H_2O_2 . The overall reaction catalyzed by peroxidases is used to reduce peroxides to water to prevent free radical formation. This process is the origin of the antioxidant properties of GSH.^{5.34}

GSH also plays a critical role in the recycling of other antioxidants such as vitamins C and E. Glutathione depletion thus leaves cells exposed to oxidative stress. For instance, GSH is known to be the primary defense mechanism of the lung.^{5.35} Pulmonary diseases can be caused from cases of low GSH concentrations, where the lung become susceptible to oxidative stress originating from the inhalation of pure oxygen, airborne toxins, and oxygen radicals produced by lung phagocytes. Similarly, oxidative stress has been shown to occur at every stage of AIDS.^{5.36} Researchers have shown that patients

with elevated levels of GSH have a greater chance of life extension than HIV-infected individuals with lower GSH levels.

5.3 Synthesis of Fluorescein Dialdehyde Derivative

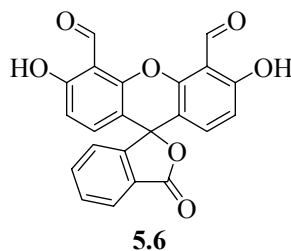
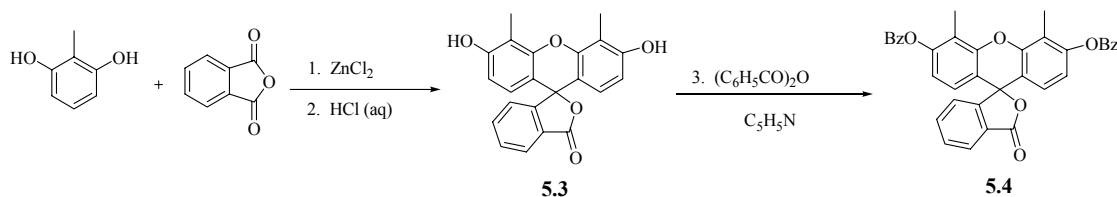


Figure 5.2 Compound **5.6**.

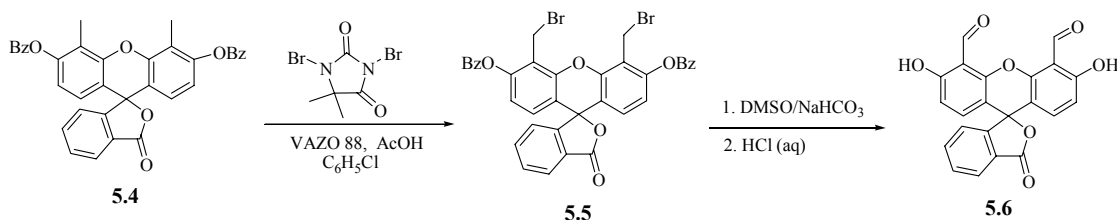
The synthesis of the fluorescein dialdehyde derivative **5.6** (Figure 5.2), was recently describe in the literature.^{5.37} Based on our work with xanthene dyes we became interested in compound **5.6**. The aldehyde moieties incorporated in compound **5.6** are very reactive and can be used as potential receptor or as a building block. I was able to synthesize **5.6** with several modifications to the literature procedure. The synthesis begins by condensing 2-methyresorcinol with phthalic anhydride via the Lewis acid ZnCl_2 to afford compound **5.3**. The intermediate **5.3** wasn't previously isolated however, is isolated here as a red solid by using aqueous HCl (6M).



Scheme 5.2 Synthesis of intermidate compound **5.4**.

This is followed by the protection of compound **5.3** with benzoic anhydride in pyridine. This provided compound **5.4** as a white crystalline solid after recrystallization using 4:1 toluene/EtOH (Scheme 5.2).

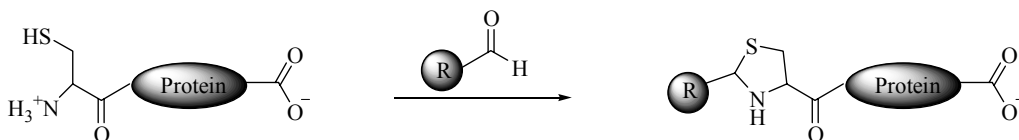
Compound **5.4** is brominated by means of 1,3-dibromo-5,5-dimethylhydantoin in C₆H₅Cl to afford compound **5.5** (**appendix**). Compound **5.5** then undergoes oxidation via DMSO followed by work-up with aqueous HCl (2M). Purification by column chromatography yields compound **5.6** (Scheme 5.3).



Scheme 5.3 Synthesis of compound **5.6** from **5.4**.

5.4 Results and Discussion

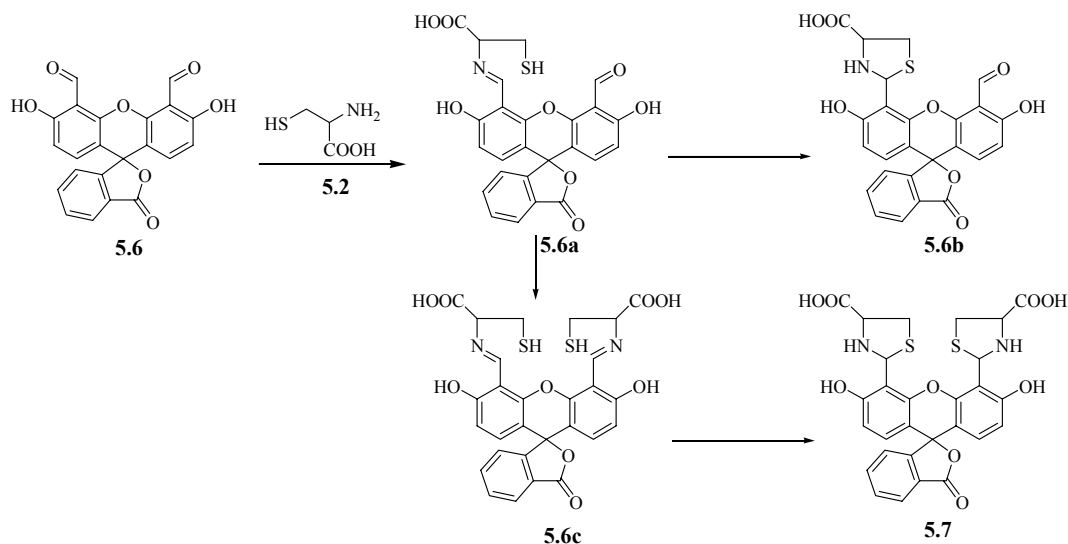
Our initial interest in compound **5.6** was derived from the interference of cysteine with known sialic acid determination.^{5.38} The colorimetric properties of **5.6** have not been previously investigated. It was employed as an intermediate towards the synthesis of a fluorescent sensor for zinc.^{5.37}



Scheme 5.4 Reaction of cysteine with aldehydes to form thiazolidines.

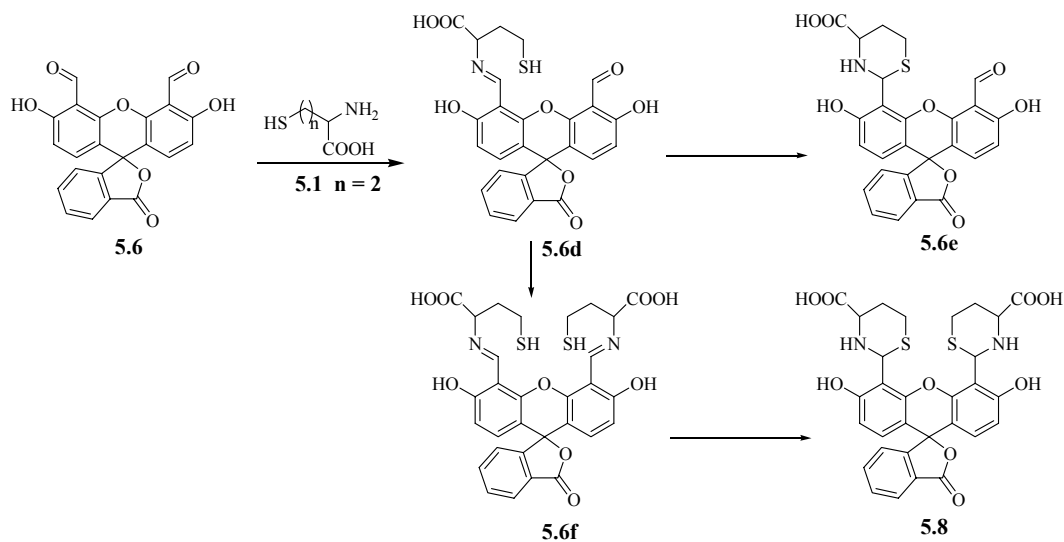
It is known that the selective reaction of *N*-terminal cysteine with aldehydes to form thiazolidines has been used to label and immobilize proteins and peptides^{5,39} (Scheme 5.4).

We reasoned that the reaction of the aldehyde moieties of **5.6** with Cys and Hcy would promote colorimetric and fluorometric responses, which would be easily monitored. The use of the xanthene dye **5.6** for the efficient detection of Cys and Hcy is presented herein. The methodology also shows promise towards the direct and simultaneous determination of both Cys and Hcy.



Scheme 5.5 Reaction of **5.6** with L-cysteine **5.2**. Reaction conditions: 0.25 M Na₂CO₃ buffer pH 9.5, followed by precipitation with MeOH.

The formation of thiazolidinic acids **5.7** and **5.8** were observed upon the reaction of **5.6** with Cys (Scheme 5.5) and Hcy (Scheme 5.6) in buffered solution. The mechanism of this process begins with initial formation of an imine (Schiff base)



Scheme 5.6 Reaction of **5.6** with L-cysteine **5.1**. Reaction conditions: 0.25 M Na₂CO₃ buffer pH 9.5, followed by precipitation with MeOH.

with subsequent cyclization into thiazolidinic acids. The thiazolidine derivatives formed were monitored by Uv-vis spectroscopy, ¹HNMR, and confirmed by MALDI TOF MS. I performed some proton NMR experiments in D₂O, using glucosamine hydrochloride and propylamine (1:2 ratio of **5.6** to analyte), which showed formation of Schiff base without cyclization. As a result diminishing aldehyde resonances are also observed at 10.2 ppm of **5.6** and the appearance of new resonances at 9.6 ppm of the Schiff base are observed. When **5.1** and **5.2** are added to solutions of **5.6**, Schiff base resonances are also observed at 9.6 ppm and disappears over time (5 min). This corresponds to the initial decrease of absorbance by UV-vis spectra. New resonances fixed at 6.13 ppm and 6.04 ppm appear, and we've assigned them to the methine protons of the thiazolidine diastereomers **5.7** and **5.8** respectively. It is evident from a 1:1 ratio of the integral areas of the new methine protons to the chromophore aromatic proton peaks that complete conversion to the bithiazolidines **5.7** and **5.8** occurred. This was confirmed by the complete disappearance

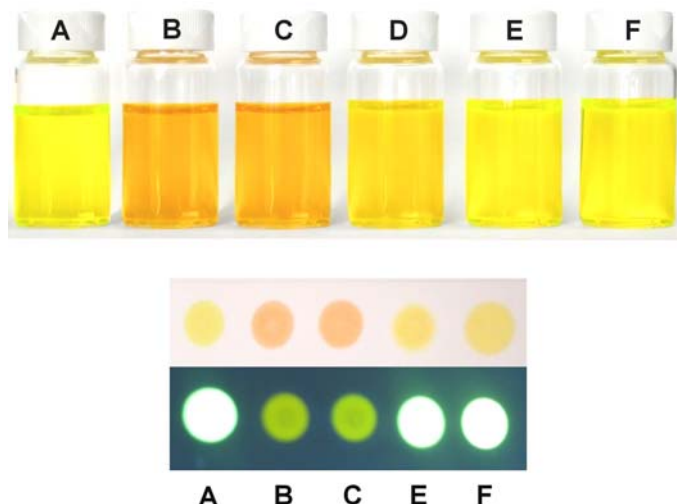


Figure 5.3 Top: color changes of solutions of **5.6** and various analytes. **A** = no analyte, **B** = L-cysteine, **C** = L-homocysteine, **D** = bovine serum albumin, **E** = L-glycine and **F** = *n*-propylamine. Bottom: co-spots of **5.6** ($1.0 \times 10^{-3} M$) with and without various analytes ($1.0 \times 10^{-3} M$) under visible and UV light.

of the starting aldehydes and intermediate Schiff base peaks. By UV-vis spectra, this corresponds to the shift in wavelength and increase in absorbance.

The visual detection of L-cysteine and L-homocysteine is seen shown below. When Cys or Hcy ($1.0 \times 10^{-3} M$) is added to a solution of **5.6** ($1.0 \times 10^{-6} M$), in H₂O at pH 9.5 using

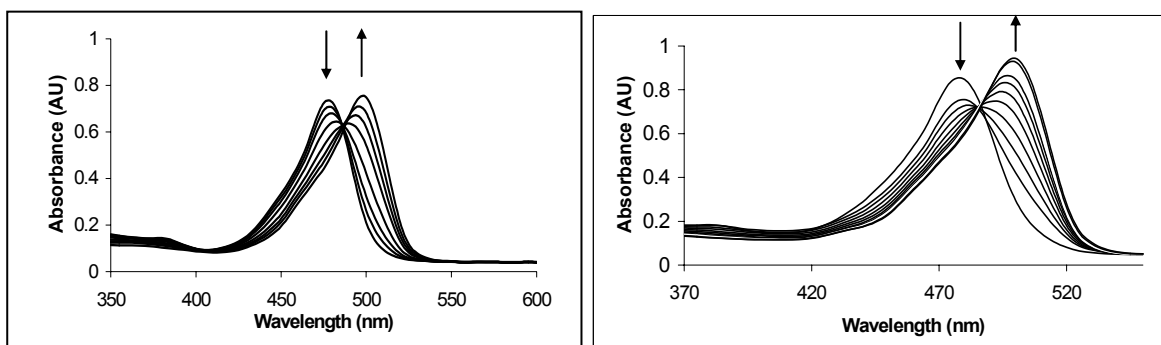


Figure 5.4 Left: Absorption spectra of dialdehyde ($2.5 \times 10^{-6} M$) and L-cysteine ($4 \times 10^{-6} M - 8 \times 10^{-5} M$) in H₂O, pH 9.5, rt, 5 min. Right: Interaction of the **5.6** ($4 \times 10^{-6} M$) and Cys (4.9×10^{-5} to $7.4 \times 10^{-4} M$) in deproteinized human blood plasma containing 5.0 mM glutathione at room temperature. Detection limit is $4 \times 10^{-5} M$.

Na_2CO_3 buffer, a solution color change is observed from bright yellow to brownish-orange. However, no significant color changes were observed, with the use of a commonly used protein, amino acid, and amine at the same concentrations. Similar effects are observed on C_{18} -bonded silica (Figure 5.3).

Figure 5.4 illustrates UV-Vis characteristic absorbance changes of cysteine-**5.6** solutions. This solution was readily monitored in the cysteine concentration range of 10^{-5} - 10^{-6} M. A decrease in absorbance at 480 nm followed by a 25 nm red shift to 505 nm with an increase in absorbance^{5,40} was displayed. This was also done using Csy in a

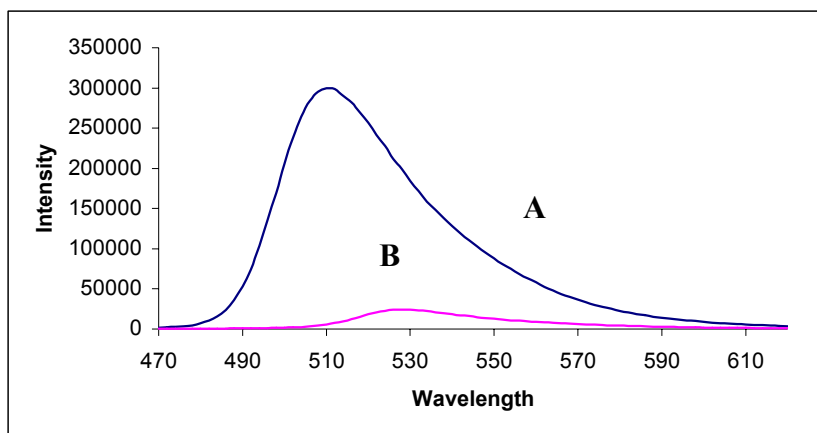


Figure 5.5 Fluorescence emission spectra of dialdehyde alone (**A**, 1.3×10^{-6} M) and after L-cysteine (3×10^{-5} M) addition (**B**), pH 9.5, rt.

sample commercial human blood plasma (previously centrifuged at 3000 g through a cellulose 3000 MW cut-off filter), containing **5.6** and excess glutathione (1 mM). This resulted in concentration-dependent spectrophotometric changes (Figure 5.4). It shows use of **5.6** for calibration and determination of concentrations of aminothiols in plasma samples in the presence of other biological thiols. Addition of L-cysteine to solutions of **5.6** results in fluorescence quenching (Figure 5.5).

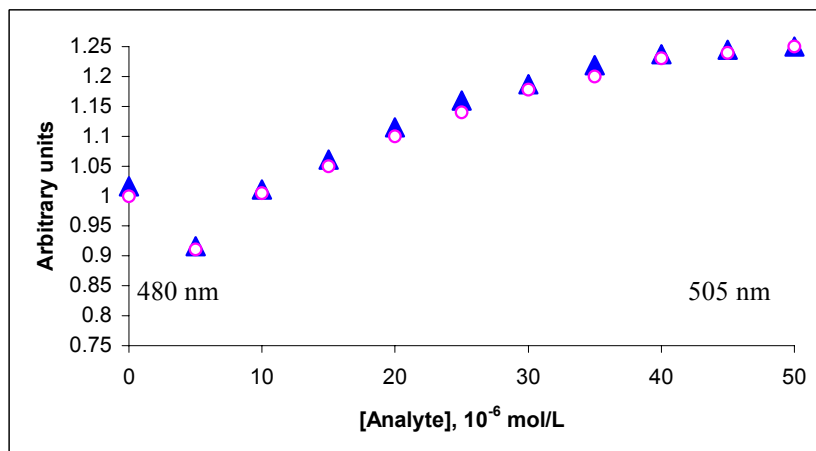


Figure 5.6 Absorbance vs. concentration plots for L-cysteine ▲ and L-homocysteine ○ in aqueous solutions of dialdehyde ($2.5 \times 10^{-6} M$) at pH 9.5.

Solutions of **5.6** containing identical concentrations of **5.1** and **5.2** exhibit similar spectrophotometric changes (Figure 5.6). An initial characteristic decrease in absorbance

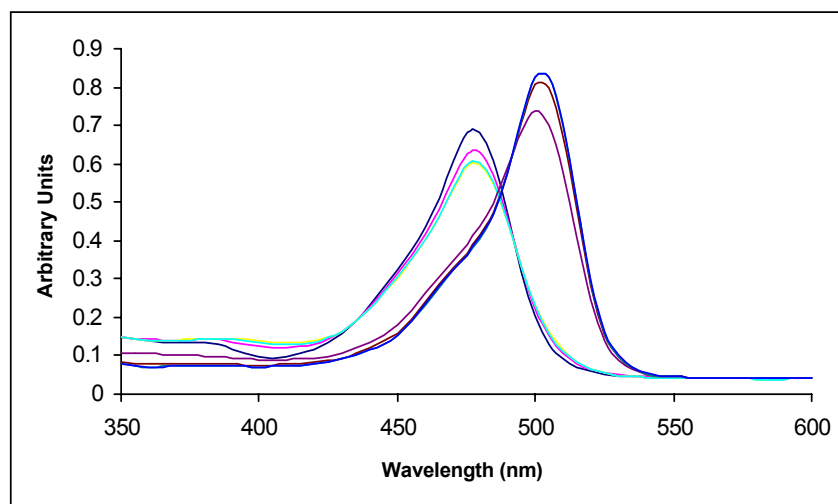


Figure 5.7 Successive addition of L-serine (to final concentrations of $4 \times 10^{-5} M$ to $8 \times 10^{-4} M$) to an aqueous solution of dialdehyde ($2.5 \times 10^{-6} M$) at pH 9.5 results only in an absorbance change at 480 nm. Addition of L-cysteine (to final concentrations of $4 \times 10^{-6} M$ - $8 \times 10^{-5} M$) to the L-serine-dialdehyde solution produces an absorbance change at 505 nm.

is observed at 480 nm, this is followed by a 25 nm red shift to 505 nm with and increase in absorbance. The selectivity of **5.6** and other common thiols (L-methionine, mercaptoethanol, glutathione), other amino acid (L-glutamine, L-serine, L-glycine, L-glutamic acid), and amines (D-glucosamine hydrochloride and *n*-propylamine (8×10^{-4} M, pH 9.5)). Only a 15% decrease in absorbance at 480 nm is observed in response to the analytes mentioned above. No wavelength shift is viewed (Figure 5.7). Another control experiment using solutions containing **5.6** and bovine serum albumin or urease also show signs of only small absorbance decrease and no wavelength shift.

We have begun to study methods, which might allow for the direct colorimetric discrimination between L-cysteine and L-homocystiene. It is known that photooxidation of cysteine-derived thiazolidines leads to fragmentation of the heterocycle.^{5,41} We are uninformed of any further studies, of those describing homocysteine-derived

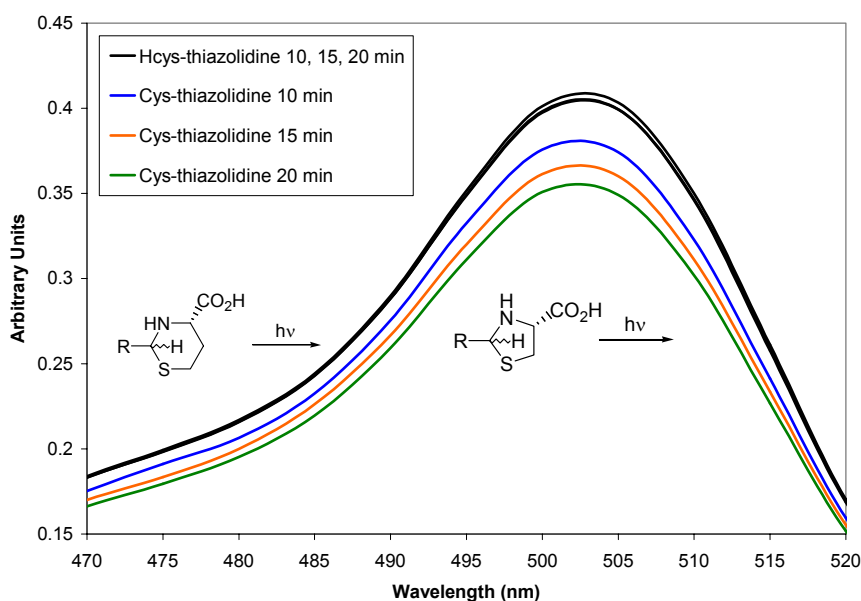


Figure 5.8 Black: UV-Vis spectra of solutions of **5.8** (1.25×10^{-5} M) after irradiation for 10, 15, and 20 min in aqueous solutions at pH 9.5. Colored: UV-Vis spectra of solutions of **5.7** (1.25×10^{-5} M) after irradiation for 10, 15, and 20 min in aqueous solutions at pH 9.5.

thiazolidines. We reasoned that the homocysteine-derived thiazolidine (**5.8**) might be more stable to photolysis than the cysteine-derived thiazolidine (**5.7**). As a result **5.7** was exposed ($1 \times 10^{-5} \text{ M}$, H_2O , pH 9.5) to a visible light source (100 W) for 10, 15 and 20 min. This showed an absorbance change at 505 nm. On the contrary, aqueous solutions of **5.8** showed no significant absorbance change when monitored at 10, 15, and 20 min (Figure 5.8)

The selectivity for the L-cysteine-derived thiazolidine **5.7** ($1.0 \times 10^{-3} \text{ M}$) is also seen in a human blood plasma, which has been centrifuged as described above. When **5.7** or **5.8** in plasma is exposed to visible light, time-dependent spectrophotometric responses at 500 nm result for plasma containing **5.8** and relatively minor responses for **5.7** (Appendix G). In contrast, a decrease in absorbance at 500 nm for the homocysteine-derived thiazolidine **5.8** was observed when solutions of 3:2 $\text{CH}_3\text{CN}:\text{H}_2\text{O}$, containing either **5.7** or **5.8** ($1 \times 10^{-3} \text{ M}$) was irradiated for 25 min with visible light. No changes in absorbance were observed for the solutions containing cysteine-derived thiazolidine **5.7**. Significantly, there is a clear selectivity observed for **5.8** in plasma when treated with CH_3CN .^{5.42, 5.43}

5.5 Conclusion

We have shown that compound **5.6** can be used to readily detect L-cysteine and L-homocysteine in the range of their physiological level. This is done with negligible interference from amines, amino acids, and certain thiols and proteins. Exposure of the thiazolidines derived from L-cysteine and L-homocysteine with a visible light, leads to absorbance changes only for the cysteine-derived thiazolidine. This may allow for the

instant detection of L-cysteine and L-homocysteine. We are currently exploring and optimizing new methods for the selective detection of L-cysteine and L-homocysteine.

5.6 Experimental

General. Matrix Assisted Laser Desorption Ionization mass spectra were acquired using a Bruker Proflex III MALDI mass spectrometer with either anthracene or dithranol matrices. UV-Visible spectra were recorded at room temperature on a Spectramax Plus (Molecular Devices). Analytical thin-layer chromatography (TLC) was performed using general-purpose silica gel on glass (Scientific Adsorbants). Flash chromatography columns were prepared with silica gel (Scientific Adsorbants, 32-63 μm particle size, 60Å). The following compounds were prepared according to literature methods: **5.4**,^{5.37} **5.5**,^{5.37} and **5.6**,^{5.37} All other chemicals were purchased from Sigma or Aldrich and used without further purification. Proton NMR spectra were acquired in either CD_3OD , CH_3OD or $\text{DMSO}-d_6$ on a Bruker DPX-250, DPX-400, or AMX-500 spectrometer. All δ values are reported with $(\text{CH}_3)_4\text{Si}$ at 0.00 ppm or DMSO at 2.45 ppm as references.

X-ray crystallographic data. Intensity data were collected on a Nonius Kappa CCD diffractometer equipped with $\text{MoK}\alpha$ radiation and a graphite monochromator. The sample was cooled to 120 K by an Oxford Cryosystems Cryostream chiller.

Compound 5.3 Phthalic anhydride (16.7 g, 113 mmol) and 2-methylresorcinol (24.9 g, 201 mmol) were crushed and melted into a brown liquid at 150 °C. Fused ZnCl_2 (15 g, 110 mmol) was added slowly over 35 min, and the temperature was slowly increased to 230 °C over 30 min until the material solidified. The brick red solid was pulverized and boiled in 400 mL of 6 M HCl for 30 min. The red solid was collected on a frit, washed thoroughly with distilled water, and dried in vacuo overnight to afford (26g, 63%). ^1H

NMR (DMSO- d_6 , 250 MHz) δ 2.27 (s, 6 H), 6.38 (d, J = 8.6 Hz, 2 H), 6.61 (d, J = 8.6 Hz, 2 H), 7.25 (d, J = 7.4 Hz, 1 H), 7.66-7.81 (m, 2 H), 7.97 (d, J = 7.3 Hz, 1 H), 8.91 (s, 1 H), 8.93 (s, 1 H). ^{13}C NMR (DMSO- d_6 , 250 MHz) δ 10.40, 111.88, 112.90, 113.70, 126.44, 126.84, 127.41, 128.57, 129.30, 132.02, 137.32, 152.39, 159.51, 170.64. MALDI m/z (anthracene matrix) calcd for $\text{C}_{22}\text{H}_{16}\text{O}_5$, 360.10 M^+ , found 360.00 M^+ .

Compound 5.7 Compound **5.6** (0.020 g, 0.0514 mmol) and cysteine (15 eq, 0.0934 g, 0.771 mmol) were added to a vial along with D_2O (1.5 mL), and NaOD (2 drops). The reaction mixture was allowed to stir overnight to yield the product as an orange sediment. ^1H NMR (D_2O , 250 MHz) δ 3.09 (t, J = 9.8 Hz, 2 H), 3.73-3.78 (m, 4 H), 6.13 (s, 1 H), 6.14 (s, 1 H), 6.46 (d, J = 9.4 Hz, 2 H), 7.02 (d, J = 9.4 Hz, 2 H), 7.15 (d, J = 6.6 Hz, 1 H), 7.43-7.54 (m, 2 H), 7.68 (d, J = 6.7 Hz, 1 H). MALDI TOF MS, calcd for $\text{C}_{28}\text{H}_{21}\text{N}_2\text{O}_9\text{S}_2\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 618.61, found 618.42.

Compound 5.8 Compound **5.6** (0.020 g, 0.0514 mmol) and cysteine (15 eq, 0.1042 g, 0.771 mmol) were added to a vial along with D_2O (1.5 mL), and NaOD (2 drops). The reaction mixture was allowed to stir overnight to yield the product as an orange sediment. ^1H NMR (D_2O , 250 MHz) δ 2.15-2.20 (m, 4 H), 2.68 (t, J = 7.6 Hz, 4 H), 3.00-3.06 (m, 4 H), 6.02 (s, 1 H), 6.06 (s, 1 H), 6.52 (d, J = 9.4 Hz, 2 H), 7.05 (d, J = 9.4 Hz, 2 H), 7.21 (d, J = 6.6 Hz, 1 H), 7.52-7.55 (m, 2 H); 7.74 (d, J = 6.0 Hz, 1 H). FAB MS, calcd for $\text{C}_{30}\text{H}_{25}\text{N}_2\text{O}_9\text{S}_2\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 646.66, found 646.80.

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CHAPTER 6

SYNTHESIS, ISOLATION, AND CHARACTERIZATION OF VARIOUS CHROMOPHORIC RECEPTORS FOR MULTIPLE FUNCTIONS

6.1 Introduction

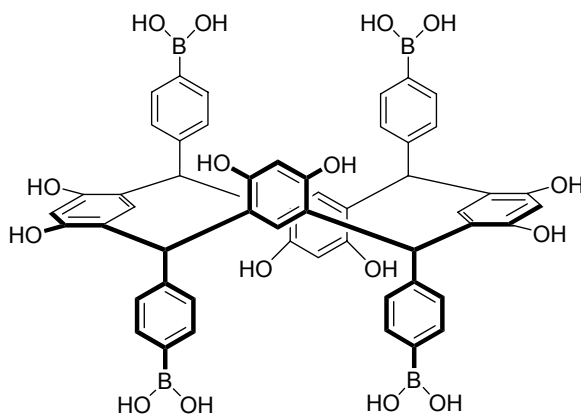
This chapter features work that has been accomplished in our laboratory, a summary of several novel receptors I synthesized, their significance, and the future direction of the Strongin research group.

6.2 Background

In 1872 von Baeyer studied the condensation of benzaldehyde and resorcinol.^{6.1} He found that a red-colored product was formed which changed color to violet in the presence of base. We have recently reported that resorcinarene receptors **6.1-6.3** (Figures 6.1 and 6.2) synthesized in our laboratories afford the most versatile color sensing of specific saccharides observed to date.^{6.2, 6.3} In this paper we reported that resorcinarenes, upon oxidation develop color due to the formation of xanthenes.^{6.4} We have also reported progress towards the selective, colorimetric and fluorimetric differentiation between L-cysteine and L-homocysteine within range of their levels in plasma.^{6.5}

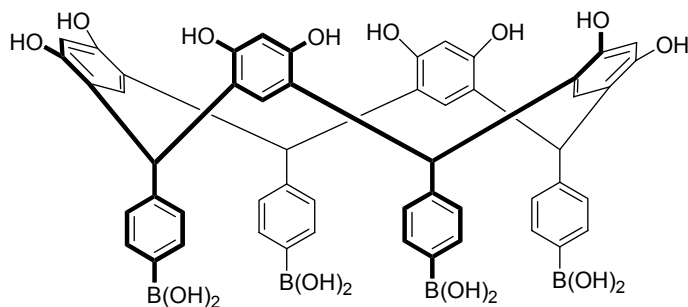
Most sugars and biological thiols are a very challenging class of compounds to analyze due to their similarity in structure. A visual sensing test for specific saccharides and thiols should allow for improved monitoring of disease states as well as the products of fermentation processes. Our preliminary studies indicate that this fundamentally new methodology could potentially have broad applicability. The exceptional color responses

to saccharides are sensitive to variations in receptor structure and experimental parameters. We can optimize both host structure and experimental conditions^{6.1,6.2} in an effort to visually sense a variety of biologically significant molecules.

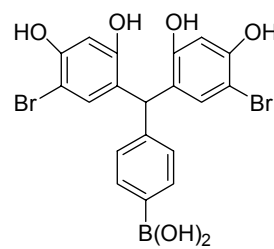


6.1

Figure 6.1 Resorcinarene colorimetric sensor.



6.2



6.3

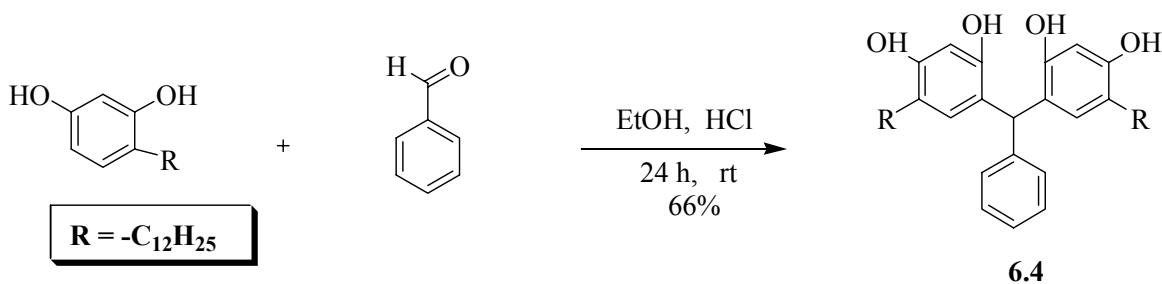
Figure 6.2 Other resorcinol-based colorimetric sensors.

6.3 Synthesis of Model Resorcinol-Base Receptors

During our investigation toward elucidating the mechanism of color formation in resorcinarene solutions, we explored the synthesis of several triaryl compounds. We

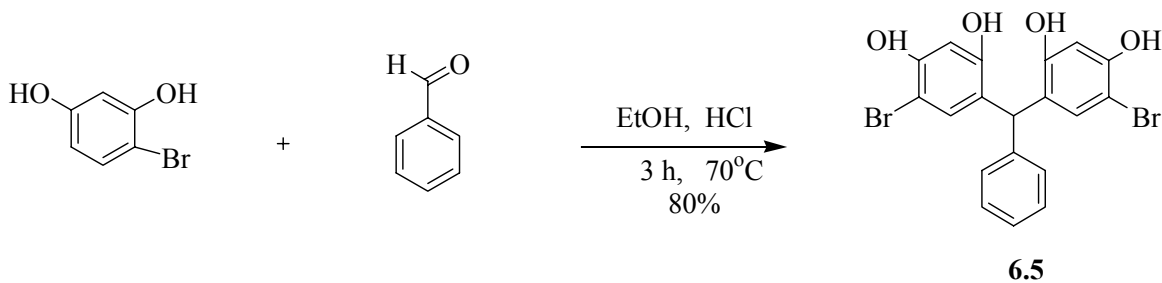
reported that heating resorcinol and phenylboronic acid alone or as a mixture in the presence of added sugars did not produce dramatic solution colors observed with **6.1**.^{6.3} To broaden the scope of the sensing process with a simple receptor, compound **6.3** was synthesized, and was found to afford vivid solution color changes.^{6.3} Based on this, I synthesized several resorcinol-based model compounds, which incorporates a variety of functional groups, with and without boronic acids.

Scheme **6.1** depicts the synthesis of the triaryl tripod, **6.4**. The synthesis involves the condensation of dodecyl resorcinol with benzaldehyde in EtOH and HCl to afford compound **6.4**. ¹H NMR, MS, and X-ray confirmed this compound (Appendix H).



Scheme 6.1 Synthesis of dodecyl tripod.

Scheme **6.2** illustrates the synthesis of another triaryl tripod that embodies a bromine-containing substructure. This involves the condensation of 4-bromoresorcinol



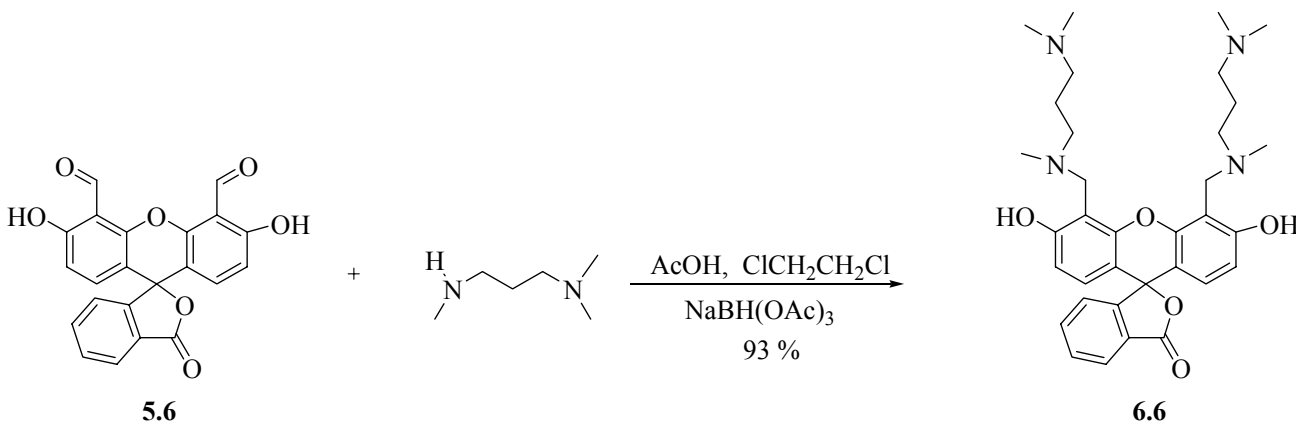
Scheme 6.2 Synthesis of bromine tripod.

with benzaldehyde in EtOH and HCl to afford compound **6.5**. Compound **6.5** was confirmed by ^1H NMR, MS, and X-ray crystal (Appendix I)

6.4 Synthesis of Fluorescein-Derived Tetraamine

Based on our work accomplished in chapter 5 with amino thiols, L-cysteine and L-homocysteine, we sought to optimize our detection method by synthesizing and studying several new dyes based on the fluorescein framework.

I was able to synthesize a fluorescein-derived tetraamine dye (TAF). The synthesis involves the condensation of the fluorescein-dialdehyde (**5.6**)^{6,6} with N,N,N'-trimethyl-1,3-propanediamine ($\text{C}_6\text{N}_2\text{H}_{14}$) in DCE. This is followed by reductive amination using $\text{NaBH}(\text{OAc})_3$ to afford compound **6.6** after work-up. Confirmation of this compound was provided by ^1H NMR and MS (Appendix J)



Scheme 6.3 Synthesis of tetraamino fluorescein (TAF).

6.5 Results and Discussion

Sialic acids generally occupy the terminal sites of glycoproteins, glycopeptides, and glycolipids. Free sialic acid also appears in biological fluids. An increase in the levels of both soluble and cellular sialic acid can be a marker for cancer diagnosis.^{6,7} The

most prevalent and significant sialic acid is *N*-acetylneuramic acid.^{6.7} The function of sialic acids in gangliosides is presently not completely understood. Sialic acids appear to be essential to the biological effects of gangliosides, as the amphiphilic donor of negative charge to the cell surface.^{6.8} A simple and rapid method for the determination of sialic acid using commercial xanthene dye may be possible.^{6.3}

Based on preliminary results, it appears that our resorcinol-based sensor **6.3** could potentially serve as a selective color-sensing agent for sialic acid (Figure 6.3). Compound **2.7**^{6.9}, **6.4**, and **6.5**, have been utilized as model compounds towards the detection of sialic acid.

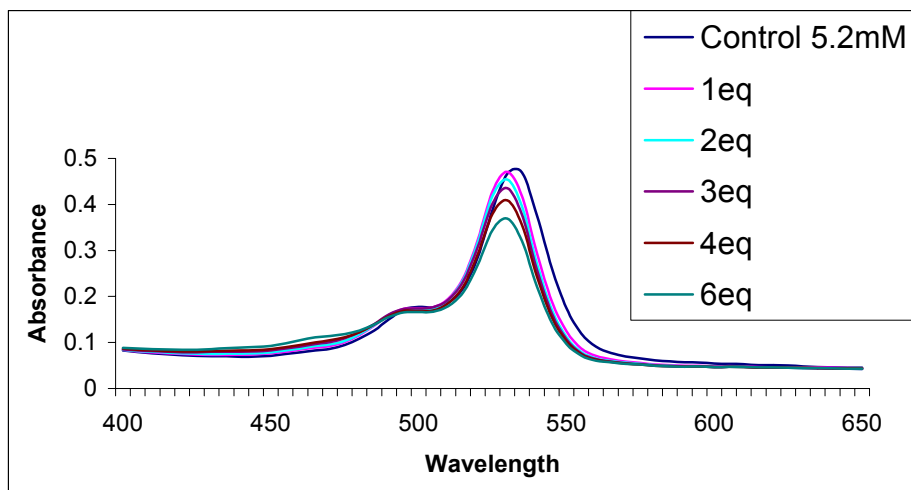


Figure 6.3 Binding between **6.3** and sialic acid. Conditions: 9:1 DMSO/H₂O, 260 mM HEPES buffer, pH 7.4.

As a result of intensive research, it was discovered that compounds **2.7** and **6.4** were not suitable model compounds due to the non-polarity of the long chain functionalities. Compound **2.7** will bind sialic acid, however the reproducibility of the experiment is very poor. The problem stems from crystal-like particles, which appears after stirring for several minutes. It is believed to be a factor of the interaction between

the hydrocarbon chain and the solvent. To date an efficient solvent system hasn't been achieved. On the other hand, compound **6.4** does not bind sialic acid. Compound **6.5** however was found to be a suitable model compound to be used as a control for compound **6.3** (Figure 6.4).

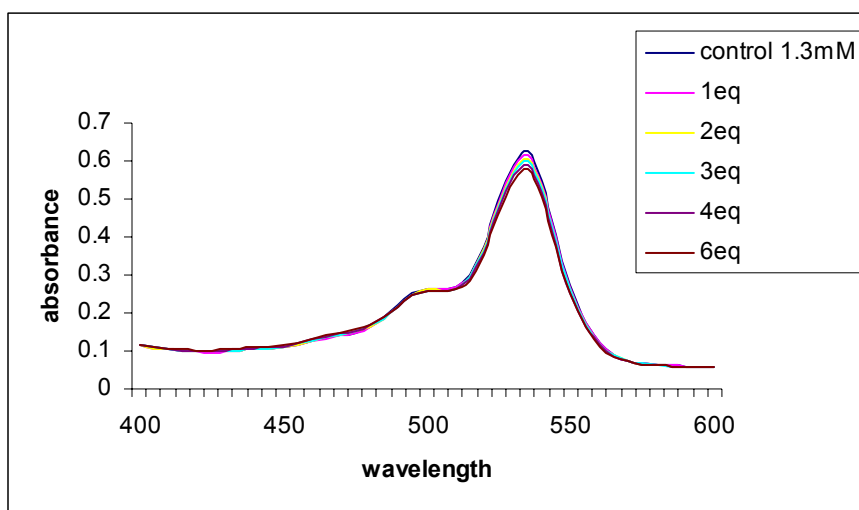


Figure 6.4 Binding of **6.5** and sialic acid. Conditions: 9:1 DMSO/H₂O, 260 mM HEPES buffer, pH 7.4.

The color is very similar to that of the compound **6.3**. However, no significant spectral responses were observed. This confirmed that the boronic acid is the key factor involved in the binding between dye and sialic acid.

Compound **6.6**, was synthesized to be utilized as a chelating agent with various inorganic metals. This may exhibit different absorbance or fluorescent degrees of selectivity for specific biological analytes. To date, five metals were examined. The complexation studies done were carried out in 0.1 M of HEPES buffer pH 7.5. Job plots for the different binary **6.6**-metal complexes reveals a range of stoichiometry (Appendix J). A screening of six different analytes was executed. This screening involved adding

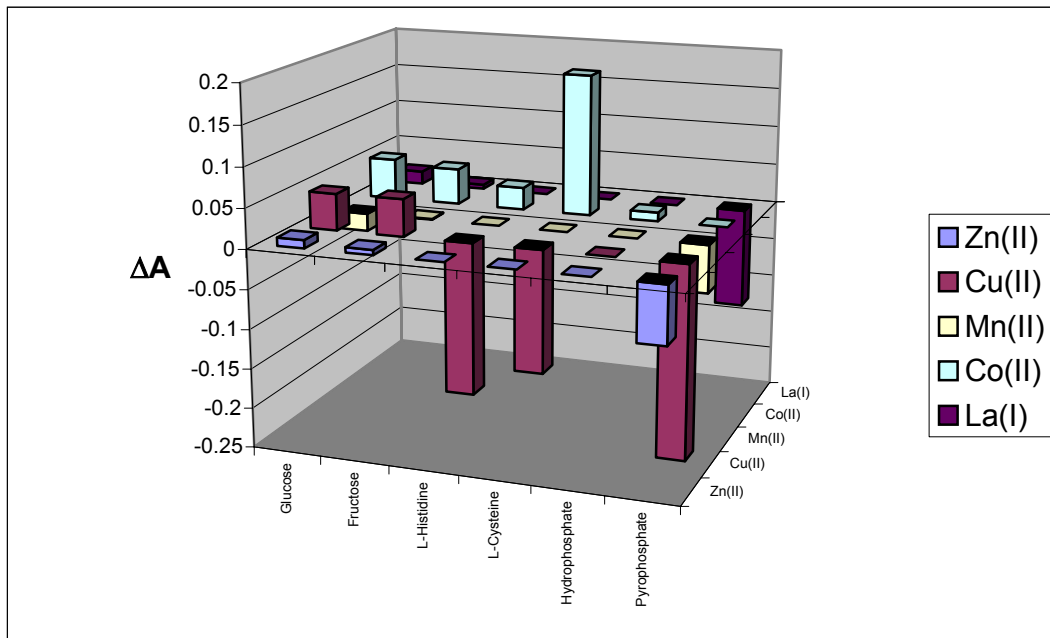


Figure 6.5 UV-Vis absorbance changes ($\lambda = 490\text{nm}$) of **6.6**-metal complexes in the presence of several saccharides, amino acids and anions.

an equimolar amount of the analyte to a solution of corresponding **6.6**-metal complex buffer (final concentration of the dye-metal complex and analyte was $1.1 \times 10^{-4} \text{ mol/L}$). Formation of the ternary complexes was monitored by UV-Vis spectroscopy and quantitatively estimated.

Figure 6.5 displays graphically the selectivity profile for **6.6**-metal complexes with the series of analytes. Control experiments demonstrate negligible absorbance responses during interaction of free **6.6** with mentioned analytes. We observe a strong significant selectivity for L-cysteine with **6.6**-Co(II), and a smaller interaction with L-histidine, D-glucose, D-fructose and hydrophosphate. Complex **6.6**-Cu(II), **6.6**-Zn(II), **6.6**-Mn(II), and **6.6**-La(I) all display an affinity for D-glucose, and D-fructose.

6.6 Conclusion and Future Work

Based on the promising results obtained with compound **6.3** and **6.4** in the first attempts; the optimization of the conditions for the selective detection of sialic acid in gangliosides, with our receptor, **6.3**, is presently being investigated.

I have presented the synthesis of a new tetraamino fluorescein dye, **6.6** which show potential application towards the detection of amino acids and anions via metal complexation. The fluorescent properties of compound **6.6** are currently being investigated in our laboratory. Our efforts are now guided towards synthesizing a library of dyes, based on the fluorescein chromophore, which will allow us to detect a variety of specific thiols. These compounds will be used to chelate different metals in an effort to enhance selectivity with saccharides, amino acids and anions.

6.7 Experimental

General. Matrix Assisted Laser Desorption Ionization mass spectra were acquired using a Bruker Proflex III MALDI mass spectrometer with either anthracene or dithranol matrices. FT-IR spectra were recorded at room temperature on a Perkin-Elmer 1760X FT-IR spectrophotometer. UV-Visible spectra were recorded at room temperature on a Spectramax Plus (Molecular Devices). Analytical thin-layer chromatography (TLC) was performed using general-purpose silica gel on glass (Scientific Adsorbants). Flash chromatography columns were prepared with silica gel (Scientific Adsorbants, 32-63 μm particle size, 60Å).

Compound 6.4. To a 100 ml three neck round bottom flask, 4-dodecylresorcinol (2.00 g, 7.18 mmol), benzaldehyde (0.365 ml, 3.59 mmol), and ethanol (30 ml) were added and stirred until clear. Concentrated HCl (15 ml) was added dropwise to the reaction mixture.

The mixture was allowed to stir at room temperature under N₂ for 24 hours. The reaction mixture was neutralized with sodium bicarbonate, and filtered. EtOH was evaporated and the compound was extracted into ethyl acetate to afford crude product (1.48 g, 66%). Flash chromatography on silica gel (85:10:5 DCM:EtOAc:MeOH) yielded the compound, as a dark brown solid. m.p. >300°C; ¹H NMR (250 MHz, DMSO-d₆) δ 1.13-1.35 (m, 46 H), 1.98-2.00 (m, 4, H), 5.81 (s, 1H), 6.27 (s, 2 H), 6.33 (s, 2 H), 6.91 (d, *J* = 7.2 Hz, 2 H), 7.06-7.16 (m, 3 H), 8.73 (s, 1 H), 8.77 (s, 1 H). ¹³C NMR (250 MHz, (DMSO-d₆) δ 15.9, 16.7, 22.8, 24.1, 30.0, 31.6, 33.4, 61.8, 104.3, 119.6, 122.7, 126.9, 129.5, 130.7, 132.9, 148.1, 154.9, 155.3, 158.2, 158.8, 159.0, 172.4. MALDI *m/z* (anthracene matrix) calcd for C₄₃H₆₄O₄ 644.9 M⁺, found 644.80 M⁺

Compound 6.5 To a 100ml three neck round bottom flask, 4-bromoresorcinol (3.00 g, 15.9 mmol), benzaldehyde (0.807 ml, 7.94 mmol), and ethanol (30 ml) were added and stirred until clear. Concentrated HCl (15 ml) was added dropwise to the mixture. The reaction mixture was allowed to stir at room temperature under N₂ for 24 h. Ethanol was removed in vacuo. This was followed by neutralization with aqueous saturated sodium bicarbonate. The compound was extracted into ethyl acetate and the solvent was evaporated. Flash chromatography on silica gel (75:25 EtOAc:hexanes - 100% EtOAc) afforded the product (2.96 g, 80%) as a brown solid. m.p. > 300 °C; ¹H NMR (250 MHz, DMSO-d₆) δ 5.72 (s, 1 H), 6.51 (s, 2 H), 6.55 (s, 2 H), 6.97 (d, *J* = 6.0 Hz, 2 H), 7.19-7.29 (m, 3 H), 9.51 (s, 2 H), 9.95 (s, 2 H); ¹³C NMR (250 MHz, (DMSO-d₆) δ 16.1, 22.9, 43.8, 61.8, 99.4, 105.6, 125.2, 130.1, 130.7, 134.3, 145.7, 154.8, 156.9; uv λ_{max} 533 nm, (DMSO/H₂O); FAB-MS (glycerol matrix) calcd for C₁₉H₁₄Br₂O₄ 466.12 M⁺, found 467.6 M⁺.

Compound 6.6. 4'5'-fluorescein-dicarboxaldehyde (200 mg, 0.514 mmol) and acetic acid (0.119 ml, 2.11 mmol) were combined in 1,2-dichloroethane (30 ml), and stirred. To the resulting solution, N, N, N'-trimethyl-1,3-propanediamine (0.158 ml, 1.08 mmol) in DCE (20 ml) was added dropwise and stirred overnight. Sodium triacetoxyborohydride (0.229 g, 1.08 mmol) was added and the reaction mixture was stirred for 12 h at room temperature. The reaction was chilled to 0 °C and H₂O was added to solution with stirring. The aqueous layer was extracted with CH₂Cl₂, and the aqueous layer was evaporated to give the product (0.28 g, 93%) as an orange solid after solvent removal. ¹H NMR (250 MHz, CD₃OD-d₄) δ 1.91-1.95 (m, 4 H), 2.40-2.44 (m, 6 H), 2.56-2.66 (m, 12 H), 2.88-3.05 (m, 8 H), 4.12 (s, 4 H), 6.60 (d, *J* = 9.3 Hz, 2 H), 7.09 (d, *J* = 9.2 Hz, 2 H), 7.23 (d, *J* = 5.0 Hz, 1 H), 7.60-7.63 (m, 2 H), 8.06 (d, *J* = 5.0 Hz, 1 H); ¹³C NMR (250 MHz, CD₃OD-d₄) δ 21.4, 22.4, 23.2, 32.6, 43.1, 43.2, 51.2, 55.4, 57.4, 61.7, 108.2, 109.9, 111.4, 112.0, 116.9, 121.6, 129.3, 129.5, 129.6, 130.1, 130.9, 131.4, 135.2, 138.9, 145.1, 149.6, 154.1, 156.0, 156.5, 157.0, 166.6, 172.6, 177.6, 179.2; ESI *m/z* calcd for C₃₄H₄₂O₅N₂ 588.33 M⁺, found 589.17 M⁺.

6.8 References

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- 6.9 Compound **2.7** was synthesized according to procedure in chapter 2, scheme 2.2.

APPENDIX A: CHARACTERIZATION DATA FOR COMPOUND 2.7

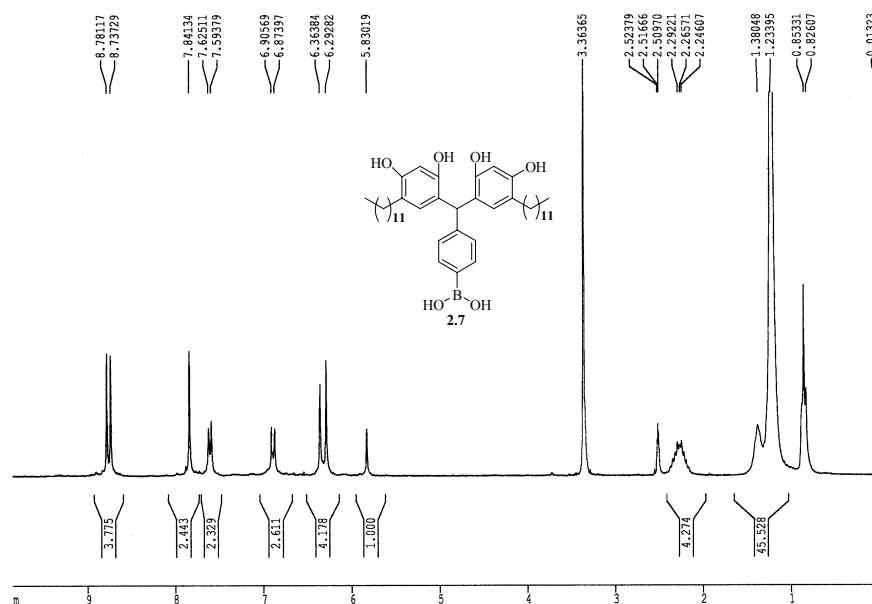


Figure A.1. ¹H NMR of compound 2.7

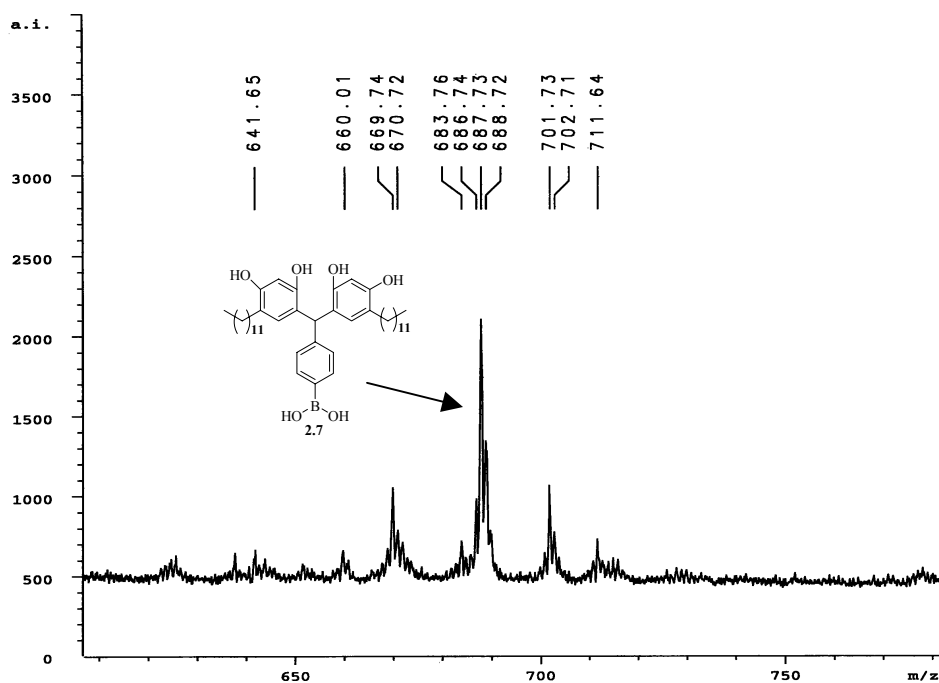


Figure A.2. MALDI MS of compound 2.7

APPENDIX B: CRYSTALLOGRAPHIC DATA FOR COMPOUND 2.7a AND ^1H NMR OF COMPOUND 2.7b.

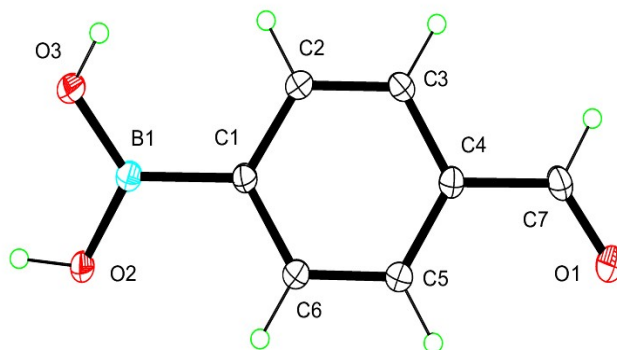


Figure B.1. Crystal structure of compound **2.7a**

Table B.1. CIF data for compound **2.7A**

CHEMICAL DATA

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'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'

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CRYSTAL DATA

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loop_

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'x+1/2, y+1/2, z'

'x+1/2, -y+1/2, z+1/2'

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REFINEMENT DATA

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Refinement of F^2 against ALL reflections. The weighted R-factor wR and

goodness of fit S are based on F^2 , conventional R-factors R are based on F , with F set to zero for negative F^2 . The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F , and R-factors based on ALL data will be even larger.

;

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_refine_ls_weighting_details
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_refine_ls_solution_secondary  difmap
_refine_ls_solution_hydrogens  geom
_refine_ls_hydrogen_treatment  mixed
_refine_ls_extinction_method    none
_refine_ls_extinction_coef      ?
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ATOMIC COORDINATES AND THERMAL PARAMETERS

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  _atom_site_adp_type
  _atom_site_occupancy
  _atom_site_symmetry_multiplicity
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 H2O H 0.390(3) 0.882(3) 0.664(4) 0.030 Uiso 1 1 d . . .
 O3 O 0.61978(12) 0.80567(12) 0.8461(2) 0.0211(3) Uani 1 1 d . . .
 H3O H 0.694(3) 0.765(3) 0.919(4) 0.032 Uiso 1 1 d . . .
 B1 B 0.5035(2) 0.72881(13) 0.7509(4) 0.0157(3) Uani 1 1 d . . .
 C1 C 0.5029(2) 0.56955(10) 0.7475(3) 0.0145(2) Uani 1 1 d . . .
 C2 C 0.61997(15) 0.49629(15) 0.7820(3) 0.0166(3) Uani 1 1 d . . .
 H2 H 0.7007 0.5436 0.8061 0.020 Uiso 1 1 calc R . .
 C3 C 0.61955(16) 0.35504(14) 0.7813(3) 0.0170(3) Uani 1 1 d . . .
 H3 H 0.6993 0.3066 0.8039 0.020 Uiso 1 1 calc R . .
 C4 C 0.5014(2) 0.28490(12) 0.7473(4) 0.0163(2) Uani 1 1 d . . .
 C5 C 0.38315(15) 0.35606(15) 0.7117(2) 0.0166(3) Uani 1 1 d . . .
 H5 H 0.3027 0.3085 0.6882 0.020 Uiso 1 1 calc R . .
 C6 C 0.38449(15) 0.49707(15) 0.7111(3) 0.0160(3) Uani 1 1 d . . .
 H6 H 0.3040 0.5453 0.6856 0.019 Uiso 1 1 calc R . .
 C7 C 0.5022(2) 0.13559(13) 0.7469(4) 0.0205(3) Uani 1 1 d . . .
 H7 H 0.5831 0.0904 0.7673 0.025 Uiso 1 1 calc R . .

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 O2 0.0149(5) 0.0105(5) 0.0293(7) 0.0001(4) 0.0062(5) 0.0002(4)
 O3 0.0133(5) 0.0141(5) 0.0287(7) 0.0002(4) 0.0044(5) -0.0010(4)
 B1 0.0148(5) 0.0125(6) 0.0178(5) -0.0001(8) 0.0064(4) -0.0008(7)
 C1 0.0141(5) 0.0115(5) 0.0160(5) 0.0009(7) 0.0059(4) 0.0006(6)
 C2 0.0139(7) 0.0149(6) 0.0195(7) -0.0005(6) 0.0071(6) -0.0016(5)
 C3 0.0142(7) 0.0138(6) 0.0212(8) -0.0004(5) 0.0073(7) 0.0024(5)
 C4 0.0168(5) 0.0118(5) 0.0193(5) -0.0007(7) 0.0079(4) -0.0004(6)
 C5 0.0145(7) 0.0144(7) 0.0200(9) 0.0009(6) 0.0076(7) 0.0000(5)
 C6 0.0140(7) 0.0137(6) 0.0188(8) 0.0000(6) 0.0068(6) -0.0005(5)
 C7 0.0193(6) 0.0118(5) 0.0276(6) -0.0007(8) 0.0092(5) 0.0029(7)

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All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

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O2 B1 1.370(2) . yes

O2 H2O 0.87(3) . ?

O3 B1 1.363(2) . yes

O3 H3O 0.83(3) . ?

B1 C1 1.5724(17) . yes

C1 C2 1.403(2) . ?

C1 C6 1.407(2) . ?

C2 C3 1.394(2) . ?

C2 H2 0.9500 . ?

C3 C4 1.398(3) . ?

C3 H3 0.9500 . ?

C4 C5 1.401(2) . ?

C4 C7 1.4740(17) . ?

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_geom_angle_atom_site_label_3

_geom_angle

_geom_angle_site_symmetry_1

_geom_angle_site_symmetry_3

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B1 O2 H2O 111.8(17) . . ?

B1 O3 H3O 117.3(19) . . ?

O3 B1 O2 117.70(11) . . yes

O3 B1 C1 124.09(16) . . yes
 O2 B1 C1 118.21(15) . . yes
 C2 C1 C6 118.39(10) . . ?
 C2 C1 B1 121.06(15) . . ?
 C6 C1 B1 120.55(16) . . ?
 C3 C2 C1 120.91(14) . . ?
 C3 C2 H2 119.5 . . ?
 C1 C2 H2 119.5 . . ?
 C2 C3 C4 119.82(15) . . ?
 C2 C3 H3 120.1 . . ?
 C4 C3 H3 120.1 . . ?
 C3 C4 C5 120.21(11) . . ?
 C3 C4 C7 119.34(18) . . ?
 C5 C4 C7 120.45(18) . . ?
 C6 C5 C4 119.43(15) . . ?
 C6 C5 H5 120.3 . . ?
 C4 C5 H5 120.3 . . ?
 C5 C6 C1 121.24(15) . . ?
 C5 C6 H6 119.4 . . ?
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 O1 C7 C4 123.21(19) . . yes
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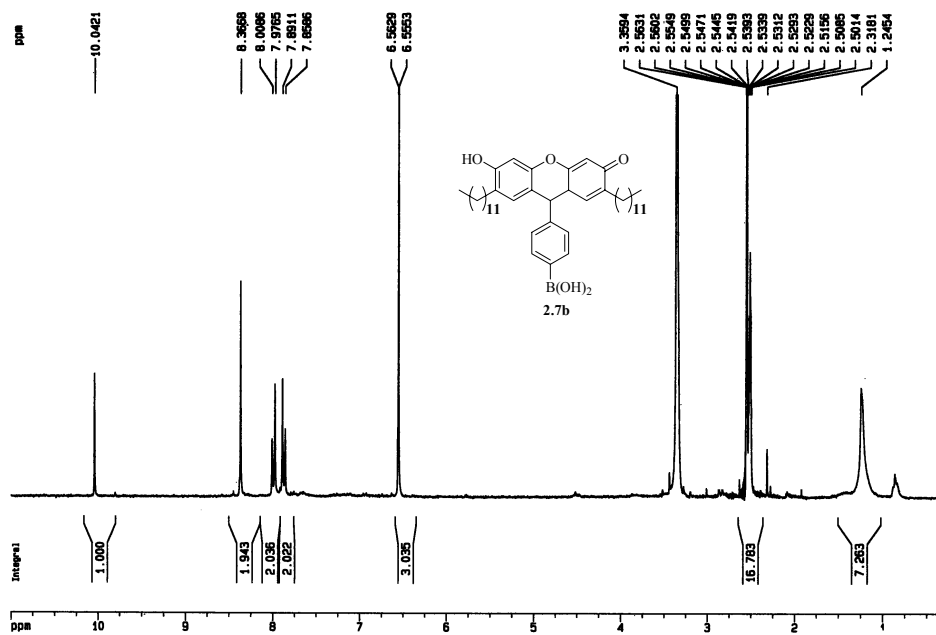
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 O2 B1 C1 C2 159.8(2) ?
 O3 B1 C1 C6 159.0(2) ?
 O2 B1 C1 C6 -20.6(3) ?
 C6 C1 C2 C3 -0.3(3) ?
 B1 C1 C2 C3 179.28(17) ?
 C1 C2 C3 C4 -0.4(3) ?
 C2 C3 C4 C5 0.7(4) ?
 C2 C3 C4 C7 180.00(18) ?
 C3 C4 C5 C6 -0.2(4) ?
 C7 C4 C5 C6 -179.48(18) ?

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C4 C5 C6 C1 -0.6(3) . . . . ?
C2 C1 C6 C5 0.8(3) . . . . ?
B1 C1 C6 C5 -178.76(16) . . . . ?
C3 C4 C7 O1 178.8(2) . . . . ?
C5 C4 C7 O1 -1.8(4) . . . . yes
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APPENDIX C: CHARACTERIZATION DATA FOR COMPOUND 3.1.

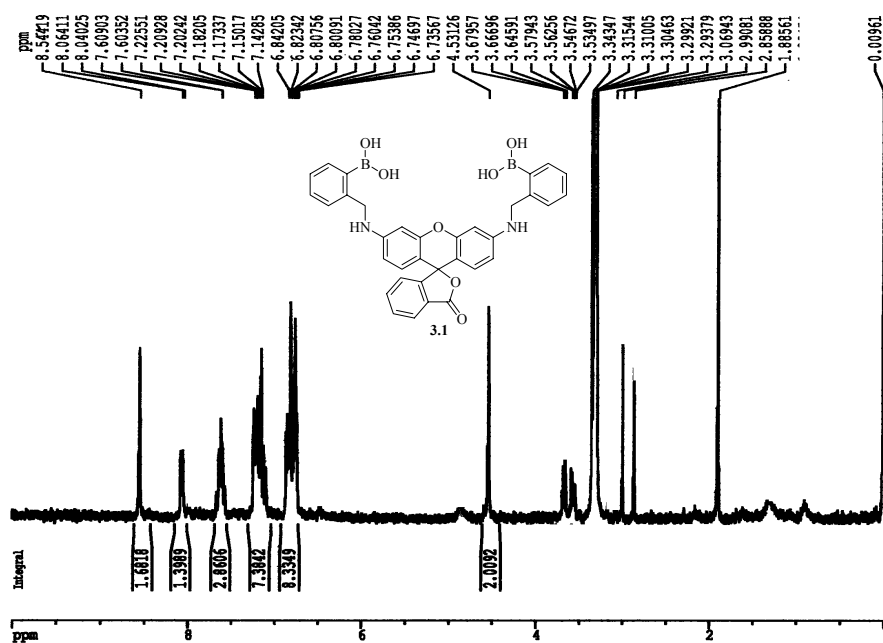


Figure C.1. ¹H NMR of compound 3.1

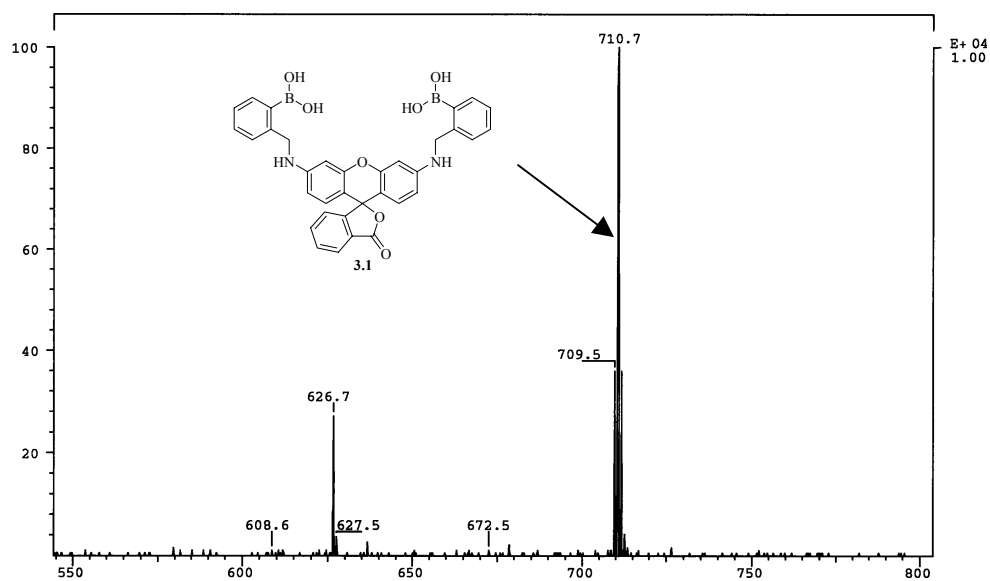


Figure C.2. FAB MS of compound 3.1

APPENDIX D: CHARACTERIZATION DATA FOR SYNTHESIS OF 4.4

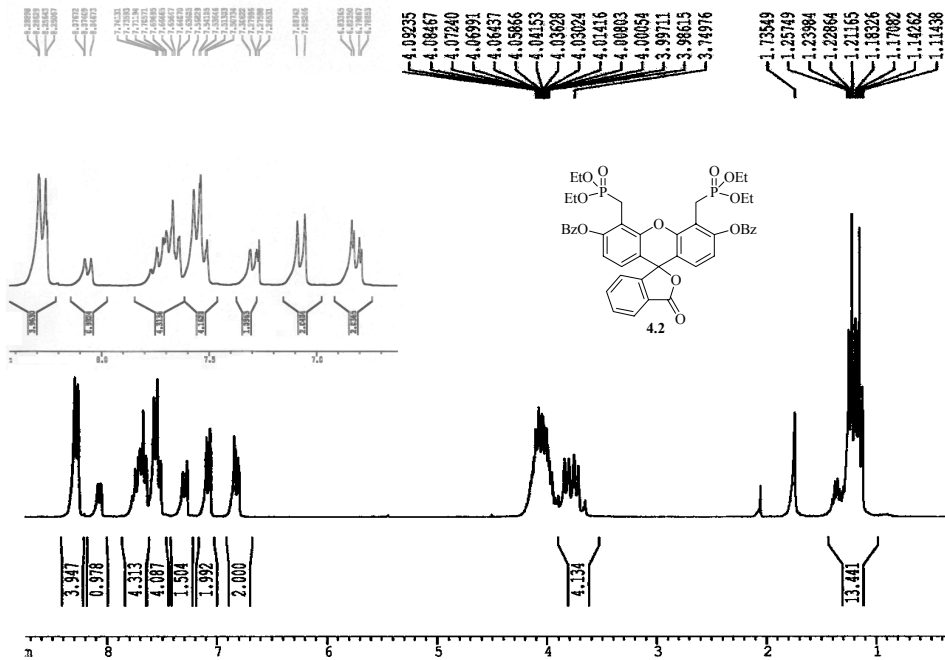


Figure D.1. ^1H NMR of compound **4.2**

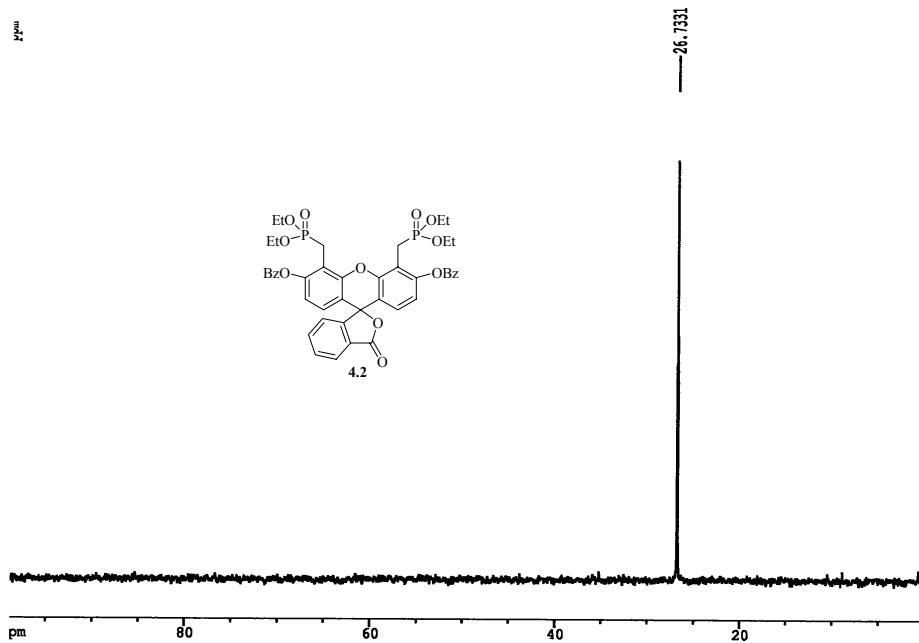


Figure D.2. ^{31}P NMR of compound **4.2**

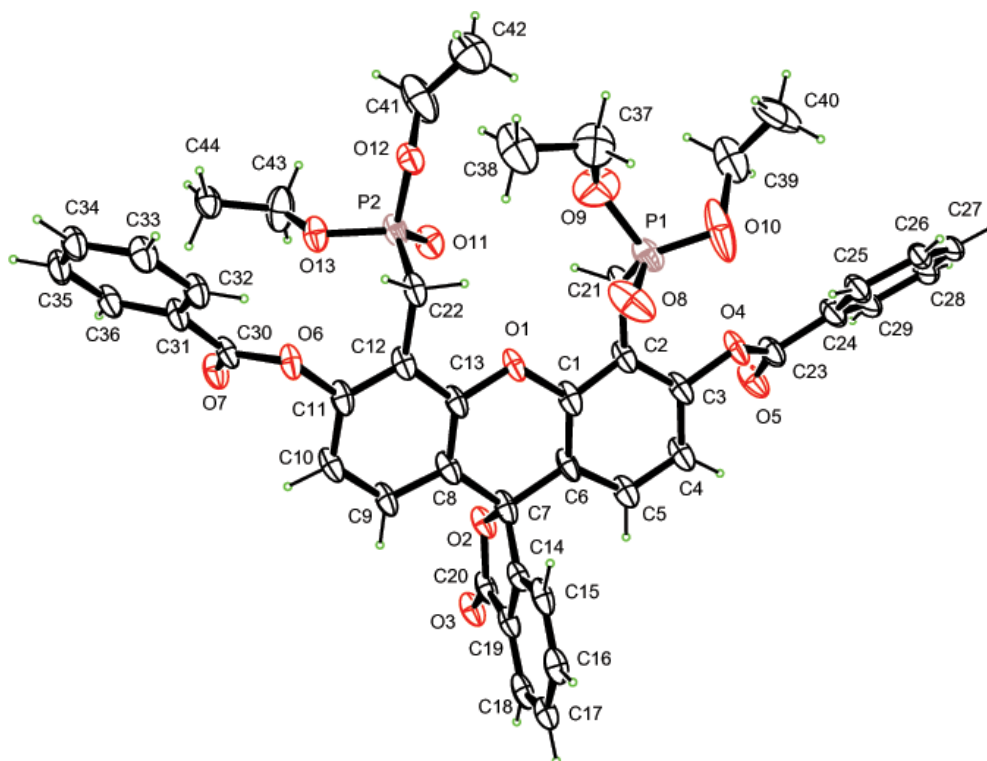


Figure D.3. Crystal structure of compound **4.2**

Table D.1. CIF data for compound **4.2**

CHEMICAL DATA

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;
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 'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
 'H' 'H' 0.0000 0.0000
 'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
 'P' 'P' 0.1023 0.0942
 'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
 'O' 'O' 0.0106 0.0060
 'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'

CRYSTAL DATA

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loop_
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 '-x+1/2, y+1/2, -z+1/2'
 '-x, -y, -z'
 'x-1/2, -y-1/2, z-1/2'

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 _cell_length_b 7.987(2)
 _cell_length_c 48.542(11)
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 _cell_angle_beta 90.336(6)
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 _cell_formula_units_Z 4
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EXPERIMENTAL DATA

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_computing_molecular_graphics 'ORTEP-3 (Farrugia, 1997)'
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Refinement of F^2 against ALL reflections. The weighted R-factor wR and goodness of fit S are based on F^2 , conventional R-factors R are based on F , with F set to zero for negative F^2 . The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F , and R-factors based on ALL data will be even larger.

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_atom_sites_solution_secondary difmap

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 O4 O 0.2467(4) 0.5269(8) 0.72146(8) 0.0838(18) Uani 1 1 d . . .
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 O6 O 0.5998(4) 0.3791(7) 0.54686(8) 0.0688(15) Uani 1 1 d . . .
 O7 O 0.4955(4) 0.1921(8) 0.52004(9) 0.0808(17) Uani 1 1 d . . .
 O8 O 0.5914(6) 0.6215(11) 0.67720(14) 0.137(3) Uani 1 1 d . . .
 O9 O 0.6727(6) 0.3373(11) 0.68548(18) 0.150(3) Uani 1 1 d . . .
 O10 O 0.5788(7) 0.5148(16) 0.72382(14) 0.186(5) Uani 1 1 d . . .
 O11 O 0.4747(4) 0.0548(7) 0.62320(10) 0.0818(17) Uani 1 1 d . . .
 O12 O 0.7180(4) 0.0654(8) 0.62457(10) 0.0814(17) Uani 1 1 d . . .
 O13 O 0.6090(4) 0.0394(7) 0.57930(9) 0.0758(16) Uani 1 1 d . . .
 C1 C 0.2962(6) 0.5101(11) 0.64792(13) 0.070(2) Uani 1 1 d . . .
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 H5 H 0.0353 0.7224 0.6492 0.088 Uiso 1 1 calc R . .
 C6 C 0.1937(6) 0.5965(11) 0.63730(12) 0.068(2) Uani 1 1 d . . .
 C7 C 0.1718(6) 0.6166(12) 0.60670(13) 0.068(2) Uani 1 1 d . . .
 C8 C 0.2840(6) 0.5440(10) 0.59061(13) 0.068(2) Uani 1 1 d . . .
 C9 C 0.2843(7) 0.5552(10) 0.56194(12) 0.070(2) Uani 1 1 d . . .
 H9 H 0.2140 0.6062 0.5527 0.084 Uiso 1 1 calc R . .
 C10 C 0.3853(7) 0.4932(11) 0.54674(14) 0.075(2) Uani 1 1 d . . .
 H10 H 0.3846 0.4988 0.5272 0.089 Uiso 1 1 calc R . .
 C11 C 0.4872(7) 0.4228(10) 0.56076(14) 0.069(2) Uani 1 1 d . . .
 C12 C 0.4927(6) 0.4065(10) 0.58905(12) 0.063(2) Uani 1 1 d . . .
 C13 C 0.3853(6) 0.4680(10) 0.60335(12) 0.065(2) Uani 1 1 d . . .
 C14 C 0.1360(6) 0.7919(11) 0.59871(12) 0.0586(19) Uani 1 1 d . . .
 C15 C 0.2053(7) 0.9419(12) 0.60141(13) 0.072(2) Uani 1 1 d . . .
 H15 H 0.2912 0.9407 0.6079 0.086 Uiso 1 1 calc R . .
 C16 C 0.1470(8) 1.0897(13) 0.59456(14) 0.076(2) Uani 1 1 d . . .
 H16 H 0.1931 1.1918 0.5960 0.092 Uiso 1 1 calc R . .
 C17 C 0.0189(7) 1.0912(11) 0.58542(13) 0.071(2) Uani 1 1 d . . .
 H17 H -0.0211 1.1946 0.5810 0.086 Uiso 1 1 calc R . .
 C18 C -0.0492(7) 0.9444(13) 0.58287(13) 0.076(3) Uani 1 1 d . . .
 H18 H -0.1354 0.9456 0.5766 0.092 Uiso 1 1 calc R . .

C19 C 0.0114(6) 0.7926(12) 0.58968(12) 0.062(2) Uani 1 1 d . . .
 C20 C -0.0369(6) 0.6209(12) 0.58927(12) 0.067(2) Uani 1 1 d . . .
 C21 C 0.4227(6) 0.3714(12) 0.68589(14) 0.078(2) Uani 1 1 d . . .
 H21A H 0.4420 0.2869 0.6716 0.093 Uiso 1 1 calc R . .
 H21B H 0.3948 0.3104 0.7026 0.093 Uiso 1 1 calc R . .
 C22 C 0.6063(6) 0.3321(10) 0.60391(12) 0.064(2) Uani 1 1 d . . .
 H22A H 0.6165 0.3881 0.6220 0.077 Uiso 1 1 calc R . .
 H22B H 0.6845 0.3541 0.5931 0.077 Uiso 1 1 calc R . .
 C23 C 0.1483(8) 0.4845(12) 0.73889(14) 0.082(3) Uani 1 1 d . . .
 C24 C 0.1905(8) 0.4923(13) 0.76804(15) 0.088(3) Uani 1 1 d . . .
 C25 C 0.3058(8) 0.5701(12) 0.77521(14) 0.089(3) Uani 1 1 d . . .
 H25 H 0.3618 0.6110 0.7614 0.107 Uiso 1 1 calc R . .
 C26 C 0.3368(9) 0.5862(13) 0.80313(16) 0.100(3) Uani 1 1 d . . .
 H26 H 0.4135 0.6410 0.8086 0.120 Uiso 1 1 calc R . .
 C27 C 0.2561(11) 0.5229(15) 0.82240(16) 0.108(4) Uani 1 1 d . . .
 H27 H 0.2781 0.5336 0.8413 0.130 Uiso 1 1 calc R . .
 C28 C 0.1451(10) 0.4448(13) 0.81547(15) 0.099(3) Uani 1 1 d . . .
 H28 H 0.0917 0.3997 0.8294 0.119 Uiso 1 1 calc R . .
 C29 C 0.1106(8) 0.4316(12) 0.78828(14) 0.091(3) Uani 1 1 d . . .
 H29 H 0.0317 0.3805 0.7833 0.109 Uiso 1 1 calc R . .
 C30 C 0.5924(7) 0.2627(10) 0.52617(13) 0.067(2) Uani 1 1 d . . .
 C31 C 0.7198(7) 0.2378(10) 0.51344(13) 0.067(2) Uani 1 1 d . . .
 C32 C 0.8277(7) 0.3218(11) 0.52255(14) 0.074(2) Uani 1 1 d . . .
 H32 H 0.8236 0.3977 0.5376 0.089 Uiso 1 1 calc R . .
 C33 C 0.9431(7) 0.2917(11) 0.50901(15) 0.079(2) Uani 1 1 d . . .
 H33 H 1.0182 0.3479 0.5151 0.095 Uiso 1 1 calc R . .
 C34 C 0.9507(8) 0.1837(12) 0.48722(15) 0.080(2) Uani 1 1 d . . .
 H34 H 1.0296 0.1678 0.4780 0.096 Uiso 1 1 calc R . .
 C35 C 0.8428(8) 0.0982(12) 0.47880(14) 0.083(3) Uani 1 1 d . . .
 H35 H 0.8481 0.0217 0.4639 0.099 Uiso 1 1 calc R . .
 C36 C 0.7287(7) 0.1223(11) 0.49166(13) 0.076(2) Uani 1 1 d . . .
 H36 H 0.6553 0.0611 0.4859 0.091 Uiso 1 1 calc R . .
 C37 C 0.8115(8) 0.3741(18) 0.6865(3) 0.147(5) Uani 1 1 d . . .
 H37A H 0.8544 0.2933 0.6989 0.177 Uiso 1 1 calc R . .
 H37B H 0.8249 0.4879 0.6941 0.177 Uiso 1 1 calc R . .
 C38 C 0.8742(9) 0.363(2) 0.6568(2) 0.152(5) Uani 1 1 d . . .
 H38A H 0.9659 0.3869 0.6583 0.228 Uiso 1 1 calc R . .
 H38B H 0.8336 0.4452 0.6446 0.228 Uiso 1 1 calc R . .
 H38C H 0.8617 0.2504 0.6493 0.228 Uiso 1 1 calc R . .
 C39 C 0.5899(13) 0.333(2) 0.7432(2) 0.148(5) Uani 1 1 d . . .
 H39A H 0.5076 0.3080 0.7523 0.178 Uiso 1 1 calc R . .
 H39B H 0.6148 0.2370 0.7316 0.178 Uiso 1 1 calc R . .
 C40 C 0.6873(13) 0.370(2) 0.7632(3) 0.183(6) Uani 1 1 d . . .
 H40A H 0.6987 0.2742 0.7755 0.275 Uiso 1 1 calc R . .
 H40B H 0.6618 0.4685 0.7740 0.275 Uiso 1 1 calc R . .
 H40C H 0.7679 0.3941 0.7538 0.275 Uiso 1 1 calc R . .

C41 C 0.7224(11) -0.105(2) 0.6402(2) 0.154(6) Uani 1 1 d . . .
 H41A H 0.6345 -0.1402 0.6449 0.185 Uiso 1 1 calc R . .
 H41B H 0.7608 -0.1915 0.6283 0.185 Uiso 1 1 calc R . .
 C42 C 0.7966(10) -0.0855(18) 0.6645(2) 0.146(5) Uani 1 1 d . . .
 H42A H 0.8013 -0.1929 0.6743 0.219 Uiso 1 1 calc R . .
 H42B H 0.7566 -0.0018 0.6765 0.219 Uiso 1 1 calc R . .
 H42C H 0.8830 -0.0487 0.6597 0.219 Uiso 1 1 calc R . .
 C43 C 0.5750(11) -0.1283(13) 0.5721(2) 0.118(4) Uani 1 1 d . . .
 H43A H 0.4806 -0.1374 0.5712 0.142 Uiso 1 1 calc R . .
 H43B H 0.6055 -0.2051 0.5867 0.142 Uiso 1 1 calc R . .
 C44 C 0.6284(7) -0.1806(12) 0.54589(14) 0.080(2) Uani 1 1 d . . .
 H44A H 0.6031 -0.2965 0.5421 0.120 Uiso 1 1 calc R . .
 H44B H 0.7219 -0.1731 0.5468 0.120 Uiso 1 1 calc R . .
 H44C H 0.5961 -0.1075 0.5312 0.120 Uiso 1 1 calc R . .

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 O1 0.046(2) 0.125(4) 0.032(2) -0.001(2) -0.0017(19) -0.022(3)
 O2 0.044(3) 0.116(4) 0.043(2) 0.002(3) -0.005(2) -0.029(3)
 O3 0.043(3) 0.141(5) 0.050(3) -0.003(3) -0.006(2) -0.028(3)
 O4 0.054(3) 0.167(6) 0.030(2) 0.004(3) 0.000(2) -0.017(3)
 O5 0.059(3) 0.188(7) 0.055(3) 0.024(3) -0.001(3) -0.020(4)
 O6 0.054(3) 0.111(4) 0.041(2) -0.014(3) 0.007(2) -0.024(3)
 O7 0.056(3) 0.134(5) 0.053(3) -0.016(3) -0.007(2) -0.024(3)
 O8 0.069(4) 0.227(9) 0.116(5) 0.066(6) -0.022(4) -0.055(5)
 O9 0.054(4) 0.177(8) 0.220(9) -0.031(6) -0.035(4) -0.012(4)
 O10 0.109(5) 0.380(15) 0.071(4) -0.069(7) 0.013(4) -0.119(7)
 O11 0.049(3) 0.128(5) 0.069(3) 0.008(3) 0.016(2) -0.021(3)
 O12 0.053(3) 0.136(5) 0.056(3) -0.001(3) 0.000(2) -0.003(3)
 O13 0.062(3) 0.108(5) 0.058(3) -0.012(3) 0.013(2) -0.030(3)
 C1 0.039(4) 0.128(7) 0.042(4) 0.000(4) 0.007(3) -0.034(4)
 C2 0.039(3) 0.122(7) 0.039(3) 0.005(4) 0.002(3) -0.026(4)
 C3 0.051(4) 0.130(7) 0.037(4) 0.011(4) -0.005(3) -0.025(4)
 C4 0.041(4) 0.151(8) 0.042(4) 0.005(4) 0.001(3) -0.020(4)
 C5 0.043(4) 0.129(7) 0.048(4) 0.003(4) 0.000(3) -0.019(4)
 C6 0.038(3) 0.133(7) 0.032(3) 0.001(4) -0.002(3) -0.026(4)
 C7 0.042(4) 0.122(7) 0.040(3) -0.007(4) -0.003(3) -0.034(4)
 C8 0.048(4) 0.115(7) 0.042(4) 0.004(4) -0.004(3) -0.032(4)

C9 0.059(4) 0.119(7) 0.033(3) 0.003(4) 0.004(3) -0.025(4)
 C10 0.066(5) 0.120(7) 0.037(4) 0.002(4) -0.007(3) -0.028(5)
 C11 0.067(5) 0.098(6) 0.042(4) -0.007(4) 0.008(3) -0.033(4)
 C12 0.048(4) 0.100(6) 0.042(4) -0.003(4) 0.002(3) -0.031(4)
 C13 0.048(4) 0.111(6) 0.035(3) 0.001(4) 0.001(3) -0.027(4)
 C14 0.047(4) 0.095(6) 0.034(3) 0.001(4) 0.000(3) -0.017(4)
 C15 0.056(4) 0.122(8) 0.037(4) -0.008(4) 0.005(3) -0.040(5)
 C16 0.078(6) 0.105(8) 0.046(4) -0.006(4) 0.009(4) -0.029(5)
 C17 0.065(5) 0.107(7) 0.042(4) -0.003(4) 0.001(3) -0.012(5)
 C18 0.054(4) 0.140(9) 0.035(4) -0.004(5) 0.006(3) -0.027(5)
 C19 0.044(4) 0.109(7) 0.034(3) -0.004(4) -0.001(3) -0.019(4)
 C20 0.041(4) 0.122(7) 0.038(4) -0.006(4) -0.003(3) -0.024(4)
 C21 0.056(4) 0.134(7) 0.042(4) 0.009(4) -0.008(3) -0.030(4)
 C22 0.039(3) 0.112(7) 0.041(3) -0.009(4) 0.006(3) -0.029(4)
 C23 0.059(5) 0.145(8) 0.043(4) 0.011(4) 0.005(4) 0.005(5)
 C24 0.070(5) 0.153(9) 0.042(4) 0.008(5) -0.005(4) 0.024(5)
 C25 0.073(5) 0.150(9) 0.045(4) -0.002(5) -0.009(4) 0.028(5)
 C26 0.095(6) 0.154(9) 0.050(5) -0.025(5) -0.022(5) 0.064(6)
 C27 0.113(8) 0.178(11) 0.033(4) -0.005(5) 0.002(5) 0.088(8)
 C28 0.099(7) 0.154(10) 0.043(4) 0.007(5) 0.012(5) 0.059(7)
 C29 0.076(5) 0.155(9) 0.041(4) 0.016(5) 0.014(4) 0.041(5)
 C30 0.069(5) 0.099(6) 0.033(3) 0.000(4) -0.006(3) -0.017(4)
 C31 0.063(5) 0.104(6) 0.034(3) -0.004(4) 0.003(3) -0.013(4)
 C32 0.063(5) 0.113(7) 0.045(4) -0.002(4) 0.008(3) -0.017(4)
 C33 0.060(5) 0.118(7) 0.060(5) -0.006(5) -0.001(4) -0.024(4)
 C34 0.068(5) 0.124(8) 0.048(4) -0.001(5) 0.009(4) -0.005(5)
 C35 0.082(6) 0.126(8) 0.040(4) -0.009(4) 0.006(4) -0.001(5)
 C36 0.073(5) 0.113(7) 0.042(4) -0.002(4) -0.005(4) -0.011(5)
 C37 0.055(5) 0.221(14) 0.165(11) -0.041(10) -0.017(6) -0.024(7)
 C38 0.067(6) 0.282(17) 0.106(8) 0.007(9) 0.007(6) -0.064(8)
 C39 0.152(11) 0.206(14) 0.086(8) -0.007(8) -0.010(7) -0.038(10)
 C40 0.185(13) 0.201(14) 0.162(12) 0.035(11) -0.119(10) -0.004(11)
 C41 0.116(9) 0.261(17) 0.085(7) 0.008(9) -0.020(6) -0.079(10)
 C42 0.100(8) 0.195(14) 0.142(11) 0.006(9) -0.023(7) -0.034(8)
 C43 0.154(10) 0.105(8) 0.097(7) -0.019(6) 0.054(7) -0.047(7)
 C44 0.065(5) 0.113(7) 0.062(5) -0.014(5) -0.007(4) -0.016(4)

_geom_special_details

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All esds (except the esd in the dihedral angle between two l.s. planes)
 are estimated using the full covariance matrix. The cell esds are taken
 into account individually in the estimation of esds in distances, angles
 and torsion angles; correlations between esds in cell parameters are only
 used when they are defined by crystal symmetry. An approximate (isotropic)
 treatment of cell esds is used for estimating esds involving l.s. planes.

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 O2 C7 1.494(7) . ?
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 O4 C3 1.401(7) . ?
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 O6 C30 1.370(8) . ?
 O6 C11 1.404(8) . ?
 O7 C30 1.195(8) . ?
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 O10 C39 1.732(17) . ?
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 C5 H5 0.9500 . ?
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 C8 C13 1.365(10) . ?
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 C9 H9 0.9500 . ?

C10 C11 1.380(10) . ?
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 C11 C12 1.380(9) . ?
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 C14 C19 1.372(9) . ?
 C14 C15 1.406(10) . ?
 C15 C16 1.369(11) . ?
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 C22 H22A 0.9900 . ?
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 C40 H40C 0.9800 . ?
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 C42 H42B 0.9800 . ?
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 C43 H43A 0.9900 . ?
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 C13 O1 C1 118.7(5) . . ?
 C20 O2 C7 110.2(6) . . ?
 C23 O4 C3 119.4(5) . . ?

C30 O6 C11 118.5(5) . . ?
 C37 O9 P1 120.8(7) . . ?
 P1 O10 C39 112.7(8) . . ?
 C41 O12 P2 117.2(5) . . ?
 C43 O13 P2 122.3(5) . . ?
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 C3 C4 C5 118.5(7) . . ?
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 C5 C4 H4 120.8 . . ?
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 C14 C7 C6 112.9(6) . . ?
 O2 C7 C8 107.1(6) . . ?
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 C8 C9 H9 119.5 . . ?
 C11 C10 C9 118.2(6) . . ?
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 C9 C10 H10 120.9 . . ?
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O1 C13 C12 113.5(6) . . ?
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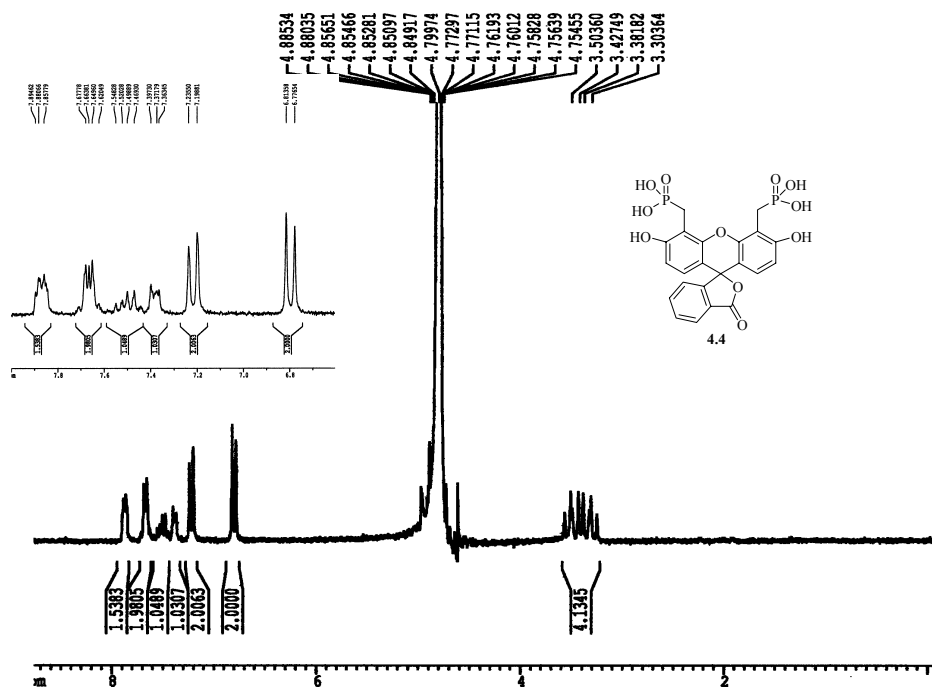


Figure D.6. ¹H NMR of compound 4.4

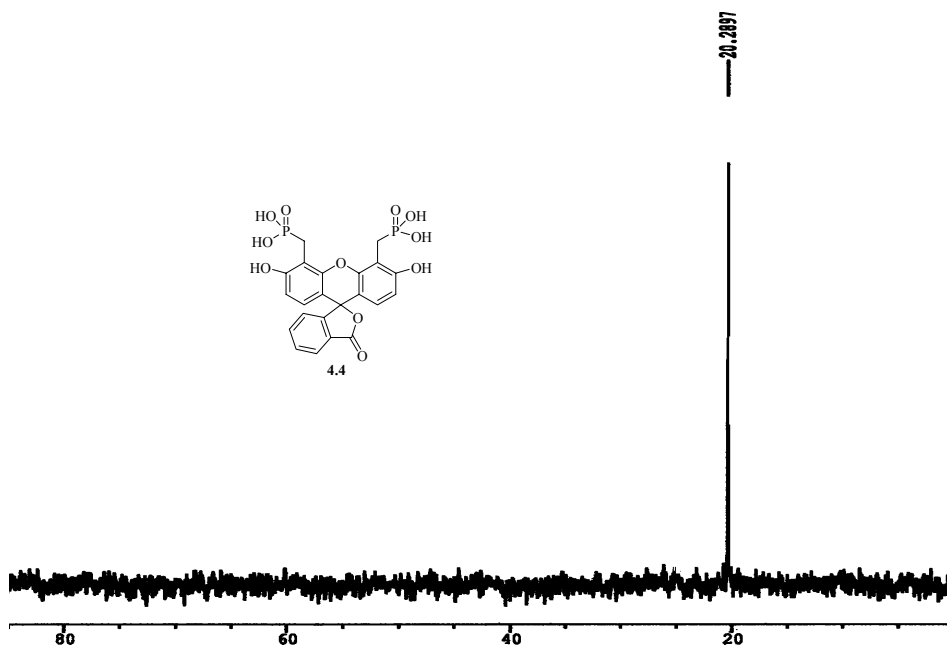


Figure D.7. ³¹P NMR of compound 4.4

APPENDIX E: JOB PLOTS RATIOS FOR 4.4-METAL COMPLEXES

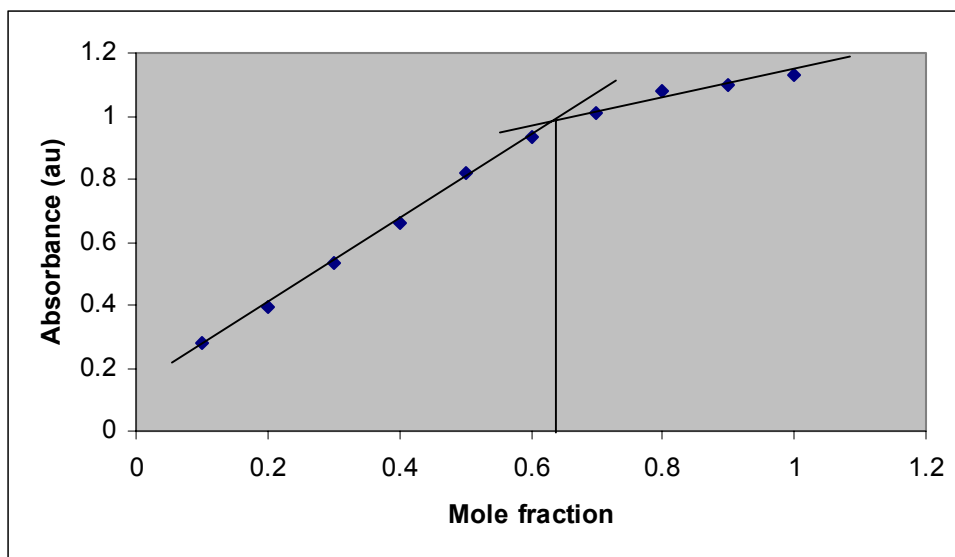


Figure E.1. A job plot for the absorbance at 500 nm of the **4.4**-Mn(II) complex. 0.1 *M* HEPES buffer, pH 7.5.

Table E.1. Stoichiometry ratio of **4.4**-metal complexes

Dye	Metal	Stoichiometry Dye:Metal
Fluorescein diphosphonate	Cu(II)	1:1
	Ni(II)	1:1
	Fe(III)	2:1
	Co(II)	1:1
	Bi(III)	1:1
	Zn(II)	2:1
	Mn(II)	2:1

APPENDIX F: MONITORING OF THIAZOLIDINIC FORMATION

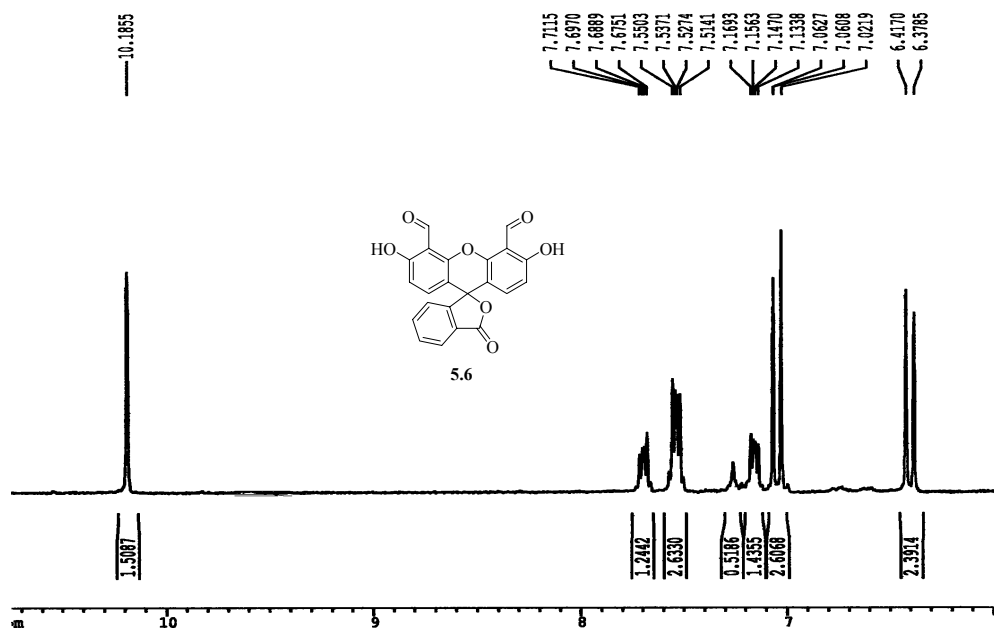


Figure F.1. ^1H NMR of compound **5.6**

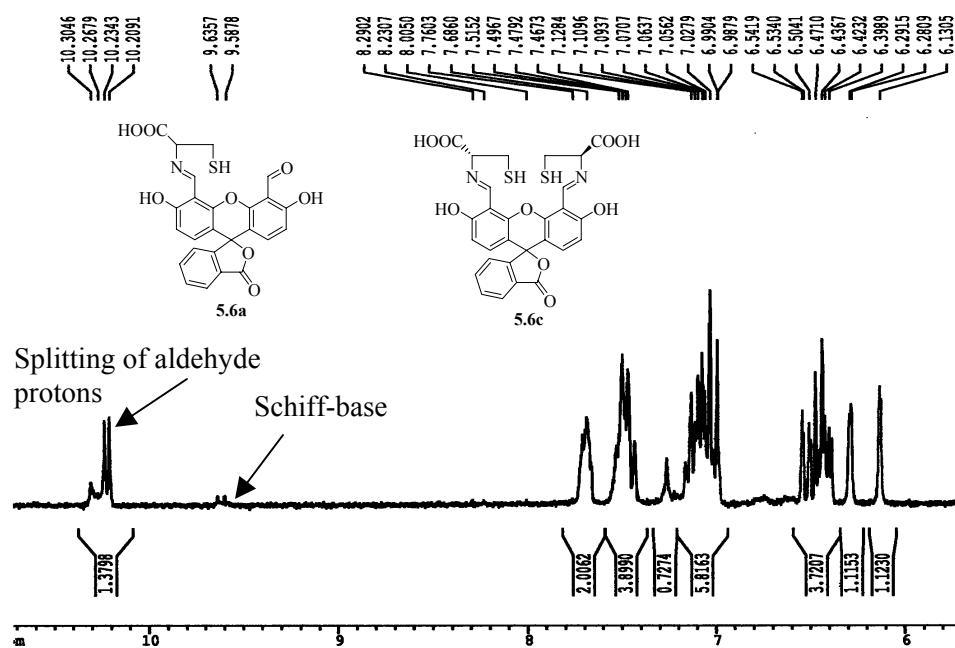


Figure F.2. ^1H NMR of intermediate compounds **5.6a** and **5.6c**

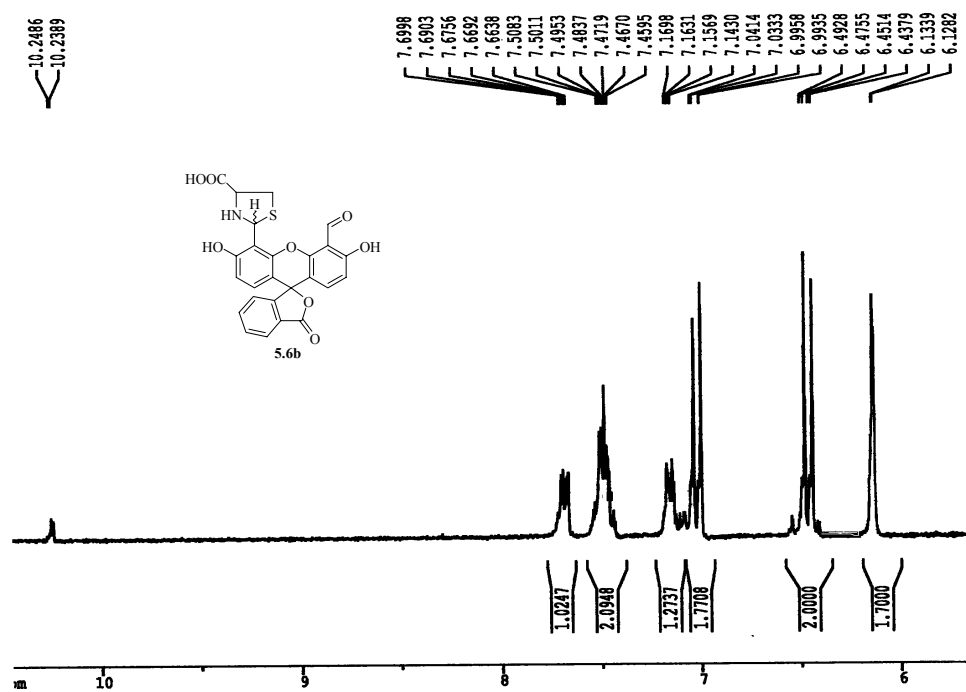


Figure F.3. ¹H NMR of intermediate compound 5.6b

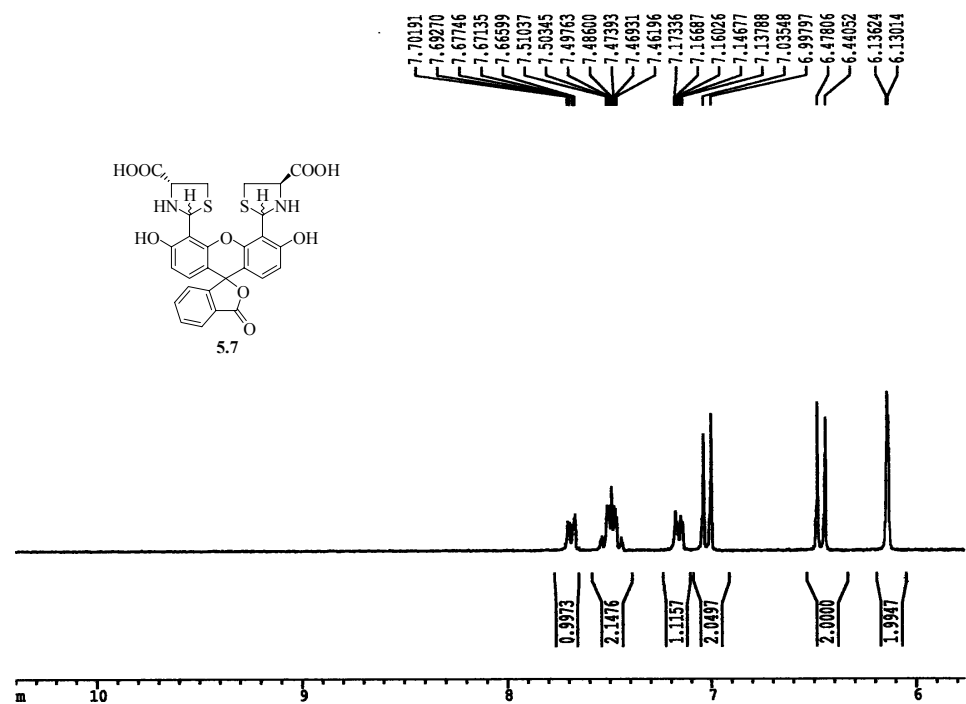


Figure F.4. ¹H NMR of compound 5.7

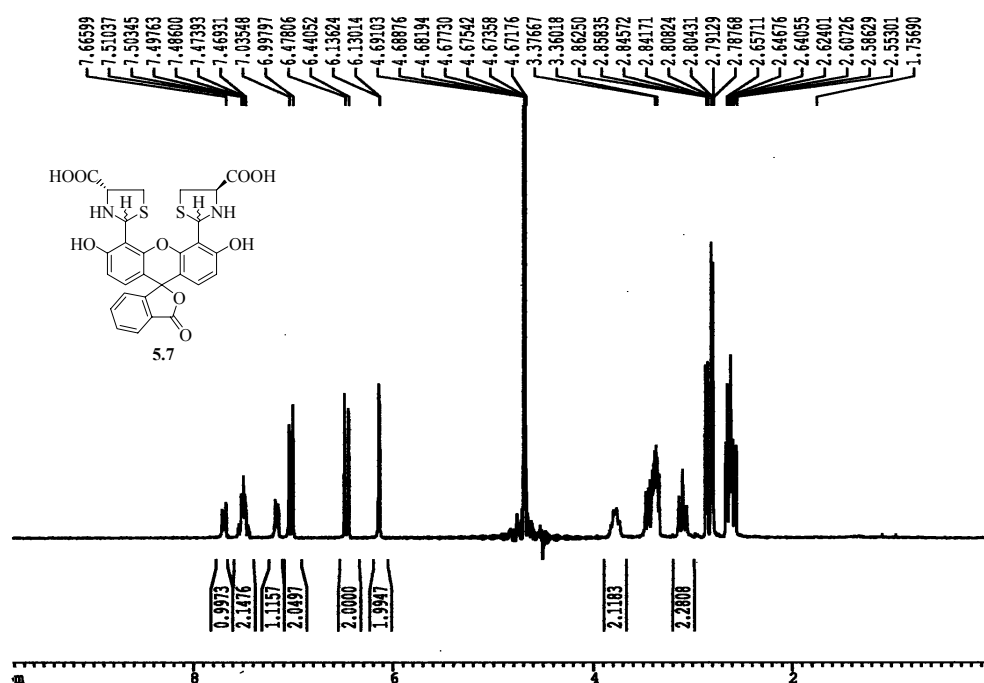


Figure F.5. Full ^1H NMR of compound 5.7

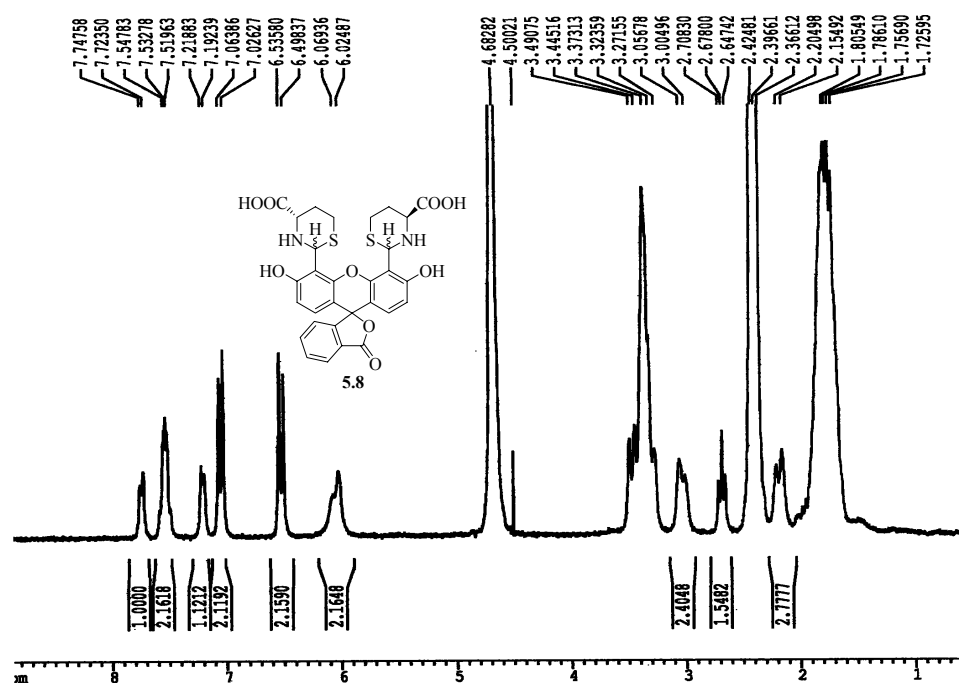


Figure F.6. Full ^1H NMR of compound 5.8

APPENDIX G: PHOTOOXIDATION OF CYSTEINE AND HOMOCYSTEINE DERIVED THIAZOLIDINE PRODUCT IN PLASMA

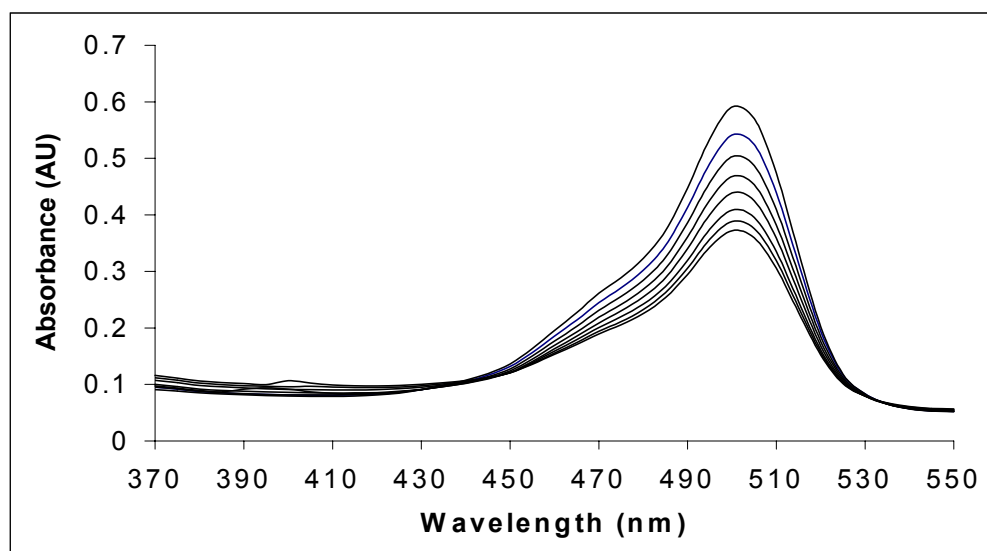


Figure G.1. Plasma deproteinized by centrifugation and filtration containing **5.7** ($1 \times 10^{-3} M$) irradiated with visible light with absorbance readings taken from 0 to 35 min.

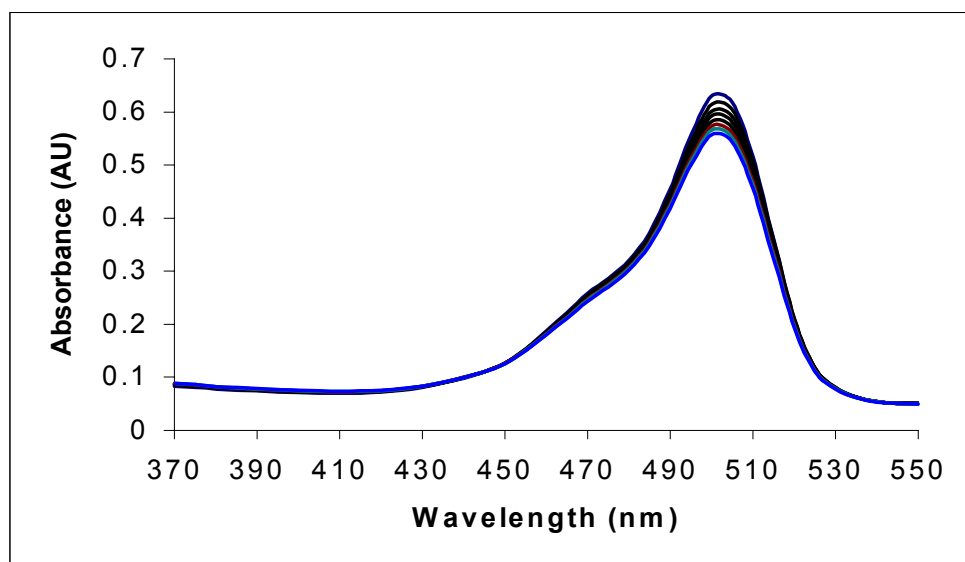


Figure G.2. Plasma deproteinized by filtration containing **5.8** ($1 \times 10^{-3} M$) irradiated with visible light with absorbance readings taken from 0 to 35 min.

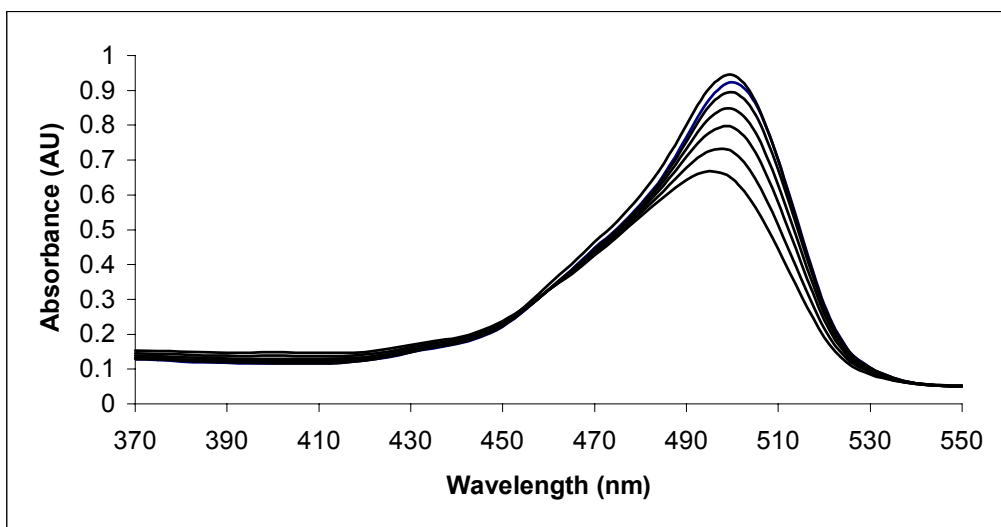


Figure G.3. Plasma deproteinized by precipitation with acetonitrile and containing **5.8** ($1 \times 10^{-3} M$). Time of irradiation by visible light is from 0 to 30 min.

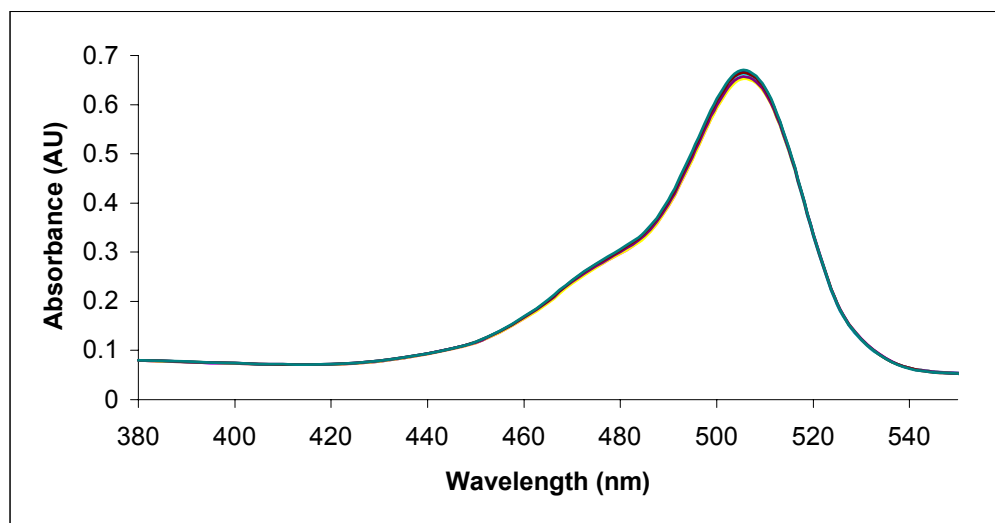


Figure G.4. Plasma deproteinized by precipitation with acetonitrile containing **5.7** ($1 \times 10^{-3} M$) irradiated with visible light with absorbance readings taken from 0 to 35 min.

APPENDIX H: CRYSTALLOGRAPHIC DATA FOR COMPOUND 5.5

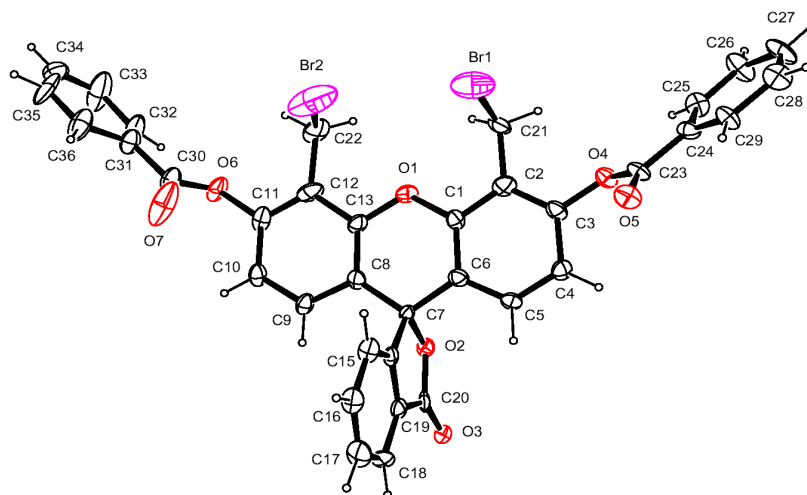


Figure H.1. Crystal structure of compound **5.5**

Table H.1. CIF data for compound **5.5**

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ATOMIC COORDINATES AND THERMAL PARAMETERS

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 Br1 Br 0.7922(2) 0.37050(10) 0.3954(2) 0.0713(11) Uiso 0.606(7) 1 d P . .
 Br2 Br 0.8685(4) 0.51824(17) 0.4598(3) 0.1113(19) Uiso 0.554(8) 1 d P . .
 O1 O 0.6515(8) 0.4586(4) 0.5579(7) 0.065(2) Uani 1 1 d . . .
 O2 O 0.5124(7) 0.4533(4) 0.8211(7) 0.055(2) Uani 1 1 d . . .
 O3 O 0.4395(9) 0.4417(3) 0.9746(7) 0.062(2) Uani 1 1 d . . .
 O4 O 0.5633(8) 0.2711(4) 0.4827(7) 0.065(2) Uani 1 1 d . . .
 O5 O 0.7368(9) 0.2203(4) 0.5847(8) 0.075(3) Uani 1 1 d . . .
 O6 O 0.7283(8) 0.6494(4) 0.5872(8) 0.073(3) Uani 1 1 d . . .
 O7 O 0.9351(11) 0.6537(5) 0.6971(14) 0.134(6) Uani 1 1 d . . .
 C1 C 0.6318(11) 0.4075(5) 0.6041(10) 0.053(3) Uani 1 1 d . . .
 C2 C 0.6139(12) 0.3642(6) 0.5221(10) 0.060(3) Uani 1 1 d . . .
 C3 C 0.5928(12) 0.3129(6) 0.5645(10) 0.057(3) Uani 1 1 d . . .
 C4 C 0.5893(11) 0.3034(6) 0.6742(10) 0.056(3) Uani 1 1 d . . .
 C5 C 0.6100(11) 0.3486(5) 0.7501(10) 0.056(3) Uani 1 1 d . . .
 H5 H 0.6104 0.3433 0.8279 0.067 Uiso 1 1 calc R . .
 C6 C 0.6297(11) 0.4006(5) 0.7133(11) 0.058(3) Uani 1 1 d . . .
 C7 C 0.6390(11) 0.4503(5) 0.7960(10) 0.049(3) Uani 1 1 d . . .
 C8 C 0.6588(10) 0.5027(5) 0.7397(10) 0.053(3) Uani 1 1 d . . .
 C9 C 0.6759(11) 0.5527(5) 0.8031(11) 0.057(3) Uani 1 1 d . . .
 H9 H 0.6714 0.5529 0.8802 0.068 Uiso 1 1 calc R . .
 C10 C 0.6996(11) 0.6025(6) 0.7514(11) 0.059(3) Uani 1 1 d . . .
 C11 C 0.7086(12) 0.5996(5) 0.6420(14) 0.066(4) Uani 1 1 d . . .
 C12 C 0.6930(13) 0.5531(7) 0.5760(11) 0.067(4) Uani 1 1 d . . .
 C13 C 0.6663(12) 0.5043(5) 0.6302(11) 0.062(4) Uani 1 1 d . . .
 C14 C 0.7372(11) 0.4423(4) 0.9145(10) 0.049(3) Uani 1 1 d . . .
 C15 C 0.8714(11) 0.4373(5) 0.9477(11) 0.056(3) Uani 1 1 d . . .
 H15 H 0.9164 0.4363 0.8915 0.068 Uiso 1 1 calc R . .
 C16 C 0.9394(14) 0.4338(6) 1.0645(13) 0.071(4) Uani 1 1 d . . .
 H16 H 1.0324 0.4300 1.0886 0.085 Uiso 1 1 calc R . .
 C17 C 0.8757(15) 0.4358(6) 1.1478(14) 0.079(5) Uani 1 1 d . . .
 H17 H 0.9255 0.4340 1.2280 0.095 Uiso 1 1 calc R . .
 C18 C 0.7411(14) 0.4402(5) 1.1154(11) 0.061(3) Uani 1 1 d . . .
 H18 H 0.6958 0.4416 1.1714 0.073 Uiso 1 1 calc R . .
 C19 C 0.6742(11) 0.4425(5) 0.9968(10) 0.049(3) Uani 1 1 d . . .
 C20 C 0.5318(13) 0.4451(5) 0.9360(11) 0.055(3) Uani 1 1 d . . .
 C21 C 0.6191(13) 0.3730(6) 0.4025(11) 0.067(4) Uani 1 1 d . . .

H21A H 0.5799 0.4093 0.3740 0.081 Uiso 1 1 calc R . .
 H21B H 0.5656 0.3444 0.3505 0.081 Uiso 1 1 calc R . .
 C22 C 0.7072(15) 0.5513(7) 0.4544(12) 0.083(5) Uani 1 1 d . . .
 H22A H 0.7034 0.5891 0.4233 0.099 Uiso 1 1 calc R . .
 H22B H 0.6334 0.5300 0.4017 0.099 Uiso 1 1 calc R . .
 C23 C 0.6423(11) 0.2259(6) 0.4984(11) 0.059(3) Uani 1 1 d . . .
 C24 C 0.5989(12) 0.1878(5) 0.4003(11) 0.058(3) Uani 1 1 d . . .
 C25 C 0.4877(12) 0.1983(6) 0.3044(12) 0.071(4) Uani 1 1 d . . .
 H25 H 0.4366 0.2304 0.3026 0.085 Uiso 1 1 calc R . .
 C26 C 0.4534(14) 0.1625(8) 0.2146(13) 0.091(5) Uani 1 1 d . . .
 H26 H 0.3775 0.1694 0.1498 0.109 Uiso 1 1 calc R . .
 C27 C 0.5278(15) 0.1161(7) 0.2165(13) 0.083(5) Uani 1 1 d . . .
 H27 H 0.5022 0.0919 0.1515 0.100 Uiso 1 1 calc R . .
 C28 C 0.6404(14) 0.1027(7) 0.3106(13) 0.083(5) Uani 1 1 d . . .
 H28 H 0.6913 0.0706 0.3117 0.099 Uiso 1 1 calc R . .
 C29 C 0.6705(13) 0.1399(6) 0.4002(11) 0.062(3) Uani 1 1 d . . .
 H29 H 0.7447 0.1326 0.4662 0.074 Uiso 1 1 calc R . .
 C30 C 0.8476(14) 0.6716(6) 0.6163(15) 0.082(5) Uani 1 1 d . . .
 C31 C 0.8570(14) 0.7189(6) 0.5442(14) 0.073(4) Uani 1 1 d . . .
 C32 C 0.749(2) 0.7448(9) 0.4744(16) 0.126(9) Uani 1 1 d . . .
 H32 H 0.6649 0.7330 0.4750 0.151 Uiso 1 1 calc R . .
 C33 C 0.758(2) 0.7875(10) 0.403(2) 0.155(11) Uani 1 1 d . . .
 H33 H 0.6802 0.8019 0.3481 0.186 Uiso 1 1 calc R . .
 C34 C 0.877(3) 0.8090(7) 0.4103(17) 0.104(6) Uani 1 1 d . . .
 H34 H 0.8842 0.8390 0.3622 0.125 Uiso 1 1 calc R . .
 C35 C 0.987(3) 0.7868(7) 0.488(3) 0.155(11) Uani 1 1 d . . .
 H35 H 1.0701 0.8014 0.4917 0.186 Uiso 1 1 calc R . .
 C36 C 0.9828(11) 0.7431(5) 0.5647(12) 0.122(8) Uani 1 1 d . . .
 H36 H 1.0585 0.7311 0.6249 0.147 Uiso 1 1 calc R . .
 Br3 Br 0.7117(11) 0.6594(5) 0.8054(12) 0.080(8) Uiso 0.092(7) 1 d PR . .
 Br4 Br 0.5294(11) 0.2337(5) 0.7083(12) 0.073(18) Uiso 0.037(6) 1 d PR . .

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 O2 0.054(5) 0.063(5) 0.046(5) 0.002(4) 0.015(4) -0.002(4)
 O3 0.074(6) 0.056(6) 0.064(6) 0.000(4) 0.033(5) -0.014(4)
 O4 0.066(5) 0.072(6) 0.051(5) -0.008(5) 0.008(4) 0.006(5)
 O5 0.069(6) 0.079(6) 0.069(6) 0.003(5) 0.010(5) 0.018(5)
 O6 0.063(6) 0.068(6) 0.074(6) 0.026(5) -0.001(4) -0.013(5)

O7 0.071(7) 0.094(9) 0.197(15) 0.071(10) -0.014(8) -0.011(6)
 C1 0.057(7) 0.056(8) 0.036(7) 0.013(6) -0.001(5) -0.012(6)
 C2 0.060(7) 0.076(9) 0.037(7) 0.004(6) 0.005(5) 0.015(7)
 C3 0.057(7) 0.066(9) 0.046(8) -0.009(7) 0.012(6) 0.000(7)
 C4 0.051(7) 0.071(9) 0.045(7) 0.001(7) 0.011(5) 0.001(6)
 C5 0.058(7) 0.068(9) 0.035(6) 0.001(6) 0.006(5) -0.006(6)
 C6 0.057(7) 0.053(8) 0.063(9) 0.003(7) 0.017(6) -0.006(6)
 C7 0.047(6) 0.048(7) 0.051(7) 0.003(6) 0.014(5) -0.010(5)
 C8 0.039(6) 0.073(9) 0.039(7) 0.011(6) 0.001(5) 0.001(6)
 C9 0.056(7) 0.049(8) 0.064(8) 0.008(7) 0.017(6) -0.004(6)
 C10 0.053(7) 0.068(9) 0.042(8) 0.018(6) -0.006(5) -0.003(6)
 C11 0.051(7) 0.047(8) 0.087(11) 0.020(8) 0.002(6) -0.008(6)
 C12 0.066(8) 0.081(11) 0.049(8) 0.031(8) 0.014(6) 0.000(7)
 C13 0.068(8) 0.054(8) 0.047(8) 0.000(7) -0.008(6) 0.005(6)
 C14 0.057(7) 0.037(6) 0.046(7) 0.010(5) 0.008(5) -0.003(5)
 C15 0.055(7) 0.051(8) 0.064(9) 0.010(6) 0.020(6) -0.002(6)
 C16 0.057(8) 0.060(9) 0.078(11) 0.000(8) -0.004(8) -0.007(7)
 C17 0.069(10) 0.079(11) 0.065(10) 0.016(8) -0.014(8) -0.010(8)
 C18 0.087(10) 0.053(7) 0.040(7) -0.001(6) 0.014(6) -0.007(7)
 C19 0.058(7) 0.044(7) 0.037(7) 0.005(5) 0.002(5) 0.002(5)
 C20 0.072(8) 0.044(7) 0.048(8) 0.000(6) 0.016(6) -0.015(6)
 C21 0.080(9) 0.073(9) 0.044(8) -0.004(7) 0.013(6) -0.007(7)
 C22 0.100(11) 0.087(11) 0.053(9) 0.034(8) 0.012(7) -0.008(9)
 C23 0.033(6) 0.082(10) 0.055(8) -0.010(7) 0.004(6) 0.012(6)
 C24 0.061(7) 0.055(8) 0.054(8) -0.003(6) 0.016(6) 0.005(6)
 C25 0.047(7) 0.079(10) 0.075(9) -0.019(8) 0.003(7) 0.009(7)
 C26 0.063(9) 0.113(14) 0.065(10) -0.020(10) -0.023(7) 0.024(9)
 C27 0.081(10) 0.092(12) 0.062(9) -0.040(8) 0.003(8) -0.005(9)
 C28 0.075(9) 0.095(11) 0.071(10) -0.010(9) 0.013(8) 0.024(9)
 C29 0.067(8) 0.067(9) 0.043(7) -0.010(6) 0.005(6) 0.007(7)
 C30 0.050(8) 0.063(9) 0.111(12) 0.035(9) -0.006(8) -0.002(7)
 C31 0.070(9) 0.063(9) 0.085(11) 0.016(8) 0.025(8) -0.001(7)
 C32 0.117(14) 0.134(18) 0.096(14) 0.069(13) -0.011(11) -0.058(13)
 C33 0.138(18) 0.137(19) 0.133(19) 0.076(16) -0.038(14) -0.071(16)
 C34 0.17(2) 0.053(10) 0.098(14) 0.016(9) 0.055(14) -0.006(13)
 C35 0.17(2) 0.044(10) 0.33(4) 0.018(16) 0.19(3) -0.013(12)
 C36 0.078(11) 0.080(12) 0.23(2) 0.026(14) 0.082(13) 0.018(9)

MOLECULAR GEOMETRY

_geom_special_details

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All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken

into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

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loop_

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Br1 C21 1.883(14) . ?

Br2 C22 1.887(17) . ?

O1 C13 1.392(16) . ?

O1 C1 1.404(14) . ?

O2 C20 1.355(14) . ?

O2 C7 1.481(13) . ?

O3 C20 1.221(14) . ?

O4 C23 1.363(15) . ?

O4 C3 1.383(15) . ?

O5 C23 1.211(14) . ?

O5 Br3 1.950(16) 2_646 ?

O6 C30 1.328(16) . ?

O6 C11 1.427(16) . ?

O7 C30 1.202(17) . ?

O7 Br4 2.23(2) 2_656 ?

C1 C6 1.340(17) . ?

C1 C2 1.417(18) . ?

C2 C3 1.393(19) . ?

C2 C21 1.482(17) . ?

C3 C4 1.360(17) . ?

C4 C5 1.404(17) . ?

C4 Br4 1.903(18) . ?

C5 C6 1.377(18) . ?

C5 H5 0.9500 . ?

C6 C7 1.551(17) . ?

C7 C8 1.490(16) . ?

C7 C14 1.500(16) . ?

C8 C13 1.353(18) . ?

C8 C9 1.418(17) . ?

C9 C10 1.421(17) . ?

C9 H9 0.9500 . ?

C10 C11 1.359(19) . ?

C10 Br3 1.517(19) . ?

C11 C12 1.36(2) . ?

C12 C13 1.427(19) . ?
 C12 C22 1.528(19) . ?
 C14 C19 1.368(17) . ?
 C14 C15 1.370(16) . ?
 C15 C16 1.373(18) . ?
 C15 H15 0.9500 . ?
 C16 C17 1.39(2) . ?
 C16 H16 0.9500 . ?
 C17 C18 1.37(2) . ?
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 C18 C19 1.389(16) . ?
 C18 H18 0.9500 . ?
 C19 C20 1.470(17) . ?
 C21 H21A 0.9900 . ?
 C21 H21B 0.9900 . ?
 C22 H22A 0.9900 . ?
 C22 H22B 0.9900 . ?
 C23 C24 1.462(18) . ?
 C24 C29 1.393(18) . ?
 C24 C25 1.399(18) . ?
 C25 C26 1.35(2) . ?
 C25 H25 0.9500 . ?
 C26 C27 1.38(2) . ?
 C26 H26 0.9500 . ?
 C27 C28 1.41(2) . ?
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 C28 C29 1.370(19) . ?
 C28 H28 0.9500 . ?
 C29 H29 0.9500 . ?
 C30 C31 1.47(2) . ?
 C31 C32 1.35(2) . ?
 C31 C36 1.418(18) . ?
 C32 C33 1.37(2) . ?
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 C34 C35 1.37(3) . ?
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 C35 C36 1.42(3) . ?
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 Br3 O5 1.950(16) 2_656 ?
 Br4 O7 2.23(2) 2_646 ?

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 C23 O4 C3 119.9(9) . . ?
 C23 O5 Br3 130.8(10) . 2_646 ?
 C30 O6 C11 119.4(10) . . ?
 C30 O7 Br4 93.8(12) . 2_656 ?
 C6 C1 C2 124.0(12) . . ?
 C6 C1 O1 123.6(12) . . ?
 C2 C1 O1 112.4(11) . . ?
 C3 C2 C1 114.1(11) . . ?
 C3 C2 C21 123.4(12) . . ?
 C1 C2 C21 122.6(13) . . ?
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 C2 C3 O4 114.8(11) . . ?
 C3 C4 C5 117.4(12) . . ?
 C3 C4 Br4 118.5(11) . . ?
 C5 C4 Br4 123.3(10) . . ?
 C4 C5 C6 121.0(11) . . ?
 C4 C5 H5 119.6 . . ?
 C6 C5 H5 119.5 . . ?
 C1 C6 C5 119.0(12) . . ?
 C1 C6 C7 121.6(11) . . ?
 C5 C6 C7 119.3(11) . . ?
 O2 C7 C8 108.9(9) . . ?
 O2 C7 C14 102.8(9) . . ?
 C8 C7 C14 113.0(9) . . ?
 O2 C7 C6 107.1(8) . . ?
 C8 C7 C6 110.9(10) . . ?
 C14 C7 C6 113.6(10) . . ?
 C13 C8 C9 117.9(12) . . ?
 C13 C8 C7 122.3(12) . . ?
 C9 C8 C7 119.7(11) . . ?
 C8 C9 C10 120.1(12) . . ?
 C8 C9 H9 120.1 . . ?
 C10 C9 H9 119.8 . . ?
 C11 C10 C9 117.6(13) . . ?
 C11 C10 Br3 116.4(11) . . ?
 C9 C10 Br3 126.0(12) . . ?
 C12 C11 C10 125.5(12) . . ?

C12 C11 O6 116.0(13) . . ?
 C10 C11 O6 118.4(13) . . ?
 C11 C12 C13 115.1(12) . . ?
 C11 C12 C22 123.9(13) . . ?
 C13 C12 C22 120.9(14) . . ?
 C8 C13 O1 124.3(12) . . ?
 C8 C13 C12 123.8(13) . . ?
 O1 C13 C12 111.9(12) . . ?
 C19 C14 C15 119.9(11) . . ?
 C19 C14 C7 109.8(10) . . ?
 C15 C14 C7 130.3(11) . . ?
 C14 C15 C16 118.3(12) . . ?
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 C14 C19 C18 122.8(12) . . ?
 C14 C19 C20 107.8(10) . . ?
 C18 C19 C20 129.4(12) . . ?
 O3 C20 O2 121.4(11) . . ?
 O3 C20 C19 129.9(11) . . ?
 O2 C20 C19 108.7(11) . . ?
 C2 C21 Br1 112.3(9) . . ?
 C2 C21 H21A 109.4 . . ?
 Br1 C21 H21A 109.1 . . ?
 C2 C21 H21B 108.9 . . ?
 Br1 C21 H21B 109.2 . . ?
 H21A C21 H21B 107.8 . . ?
 C12 C22 Br2 110.3(9) . . ?
 C12 C22 H22A 109.3 . . ?
 Br2 C22 H22A 109.3 . . ?
 C12 C22 H22B 109.7 . . ?
 Br2 C22 H22B 110.1 . . ?
 H22A C22 H22B 108.2 . . ?
 O5 C23 O4 121.6(12) . . ?
 O5 C23 C24 126.6(12) . . ?
 O4 C23 C24 111.8(10) . . ?
 C29 C24 C25 118.4(12) . . ?
 C29 C24 C23 119.7(11) . . ?

C25 C24 C23 122.0(12) . . ?
 C26 C25 C24 119.8(13) . . ?
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 C24 C25 H25 120.3 . . ?
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 C25 C26 H26 119.8 . . ?
 C27 C26 H26 119.9 . . ?
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 C29 C28 C27 114.6(14) . . ?
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 C27 C28 H28 122.7 . . ?
 C28 C29 C24 124.0(12) . . ?
 C28 C29 H29 117.9 . . ?
 C24 C29 H29 118.1 . . ?
 O7 C30 O6 120.5(13) . . ?
 O7 C30 C31 125.9(14) . . ?
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 C31 C32 C33 122.3(19) . . ?
 C31 C32 H32 119.0 . . ?
 C33 C32 H32 118.7 . . ?
 C34 C33 C32 119.7(19) . . ?
 C34 C33 H33 119.6 . . ?
 C32 C33 H33 120.7 . . ?
 C33 C34 C35 118.7(16) . . ?
 C33 C34 H34 121.1 . . ?
 C35 C34 H34 120.2 . . ?
 C34 C35 C36 123.6(17) . . ?
 C34 C35 H35 118.6 . . ?
 C36 C35 H35 117.8 . . ?
 C35 C36 C31 114.7(16) . . ?
 C35 C36 H36 123.0 . . ?
 C31 C36 H36 122.2 . . ?
 C10 Br3 O5 162.4(10) . 2_656 ?
 C4 Br4 O7 151.0(8) . 2_646 ?

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 C13 O1 C1 C6 -1.7(17) ?
 C13 O1 C1 C2 178.1(10) ?
 C6 C1 C2 C3 0.4(18) ?
 O1 C1 C2 C3 -179.4(10) ?
 C6 C1 C2 C21 -179.0(12) ?
 O1 C1 C2 C21 1.2(17) ?
 C1 C2 C3 C4 -0.2(18) ?
 C21 C2 C3 C4 179.1(12) ?
 C1 C2 C3 O4 174.4(10) ?
 C21 C2 C3 O4 -6.3(18) ?
 C23 O4 C3 C4 -64.8(15) ?
 C23 O4 C3 C2 120.4(13) ?
 C2 C3 C4 C5 -0.7(18) ?
 O4 C3 C4 C5 -175.1(10) ?
 C2 C3 C4 Br4 169.3(11) ?
 O4 C3 C4 Br4 -5.0(16) ?
 C3 C4 C5 C6 1.6(17) ?
 Br4 C4 C5 C6 -167.9(10) ?
 C2 C1 C6 C5 0.4(19) ?
 O1 C1 C6 C5 -179.8(10) ?
 C2 C1 C6 C7 -175.2(11) ?
 O1 C1 C6 C7 4.6(18) ?
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 C4 C5 C6 C7 174.2(10) ?
 C20 O2 C7 C8 -123.2(10) ?
 C20 O2 C7 C14 -3.2(11) ?
 C20 O2 C7 C6 116.8(10) ?
 C1 C6 C7 O2 114.9(12) ?
 C5 C6 C7 O2 -60.7(13) ?
 C1 C6 C7 C8 -3.8(15) ?
 C5 C6 C7 C8 -179.3(10) ?
 C1 C6 C7 C14 -132.3(12) ?
 C5 C6 C7 C14 52.1(14) ?
 O2 C7 C8 C13 -117.3(12) ?
 C14 C7 C8 C13 129.2(12) ?
 C6 C7 C8 C13 0.3(15) ?
 O2 C7 C8 C9 65.3(12) ?
 C14 C7 C8 C9 -48.2(14) ?
 C6 C7 C8 C9 -177.1(10) ?
 C13 C8 C9 C10 0.2(17) ?
 C7 C8 C9 C10 177.7(10) ?

C8 C9 C10 C11 -1.8(17) ?
 C8 C9 C10 Br3 176.2(10) ?
 C9 C10 C11 C12 2.0(19) ?
 Br3 C10 C11 C12 -176.1(12) ?
 C9 C10 C11 O6 178.1(10) ?
 Br3 C10 C11 O6 -0.1(16) ?
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 C30 O6 C11 C10 78.3(17) ?
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 C9 C8 C13 O1 -180.0(10) ?
 C7 C8 C13 O1 2.5(18) ?
 C9 C8 C13 C12 1.4(18) ?
 C7 C8 C13 C12 -176.1(11) ?
 C1 O1 C13 C8 -2.1(17) ?
 C1 O1 C13 C12 176.7(10) ?
 C11 C12 C13 C8 -1.2(19) ?
 C22 C12 C13 C8 176.8(12) ?
 C11 C12 C13 O1 -180.0(11) ?
 C22 C12 C13 O1 -2.0(17) ?
 O2 C7 C14 C19 -1.6(12) ?
 C8 C7 C14 C19 115.5(11) ?
 C6 C7 C14 C19 -117.0(11) ?
 O2 C7 C14 C15 -179.2(11) ?
 C8 C7 C14 C15 -62.0(16) ?
 C6 C7 C14 C15 65.4(16) ?
 C19 C14 C15 C16 -1.5(18) ?
 C7 C14 C15 C16 175.9(12) ?
 C14 C15 C16 C17 -1(2) ?
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 C15 C14 C19 C18 2.9(18) ?
 C7 C14 C19 C18 -174.9(10) ?
 C15 C14 C19 C20 -176.7(10) ?
 C7 C14 C19 C20 5.4(13) ?
 C17 C18 C19 C14 -2.1(18) ?
 C17 C18 C19 C20 177.4(13) ?
 C7 O2 C20 O3 -174.5(10) ?
 C7 O2 C20 C19 6.5(12) ?
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 C14 C19 C20 O2 -7.5(13) ?
 C18 C19 C20 O2 172.9(11) ?
 C3 C2 C21 Br1 -94.1(14) ?

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 Br3 O5 C23 O4 127.7(13) 2_646 . . . ?
 Br3 O5 C23 C24 -53.1(19) 2_646 . . . ?
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 C3 O4 C23 C24 -177.2(11) ?
 O5 C23 C24 C29 -1(2) ?
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 O5 C23 C24 C25 -180.0(13) ?
 O4 C23 C24 C25 -0.7(18) ?
 C29 C24 C25 C26 -1(2) ?
 C23 C24 C25 C26 178.4(15) ?
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 C27 C28 C29 C24 -1(2) ?
 C25 C24 C29 C28 1(2) ?
 C23 C24 C29 C28 -177.6(14) ?
 Br4 O7 C30 O6 -121.7(16) 2_656 . . . ?
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 C11 O6 C30 O7 -8(3) ?
 C11 O6 C30 C31 173.4(14) ?
 O7 C30 C31 C32 -163(2) ?
 O6 C30 C31 C32 15(3) ?
 O7 C30 C31 C36 6(3) ?
 O6 C30 C31 C36 -176.4(14) ?
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 C31 C32 C33 C34 -8(4) ?
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 C33 C34 C35 C36 -2(4) ?
 C34 C35 C36 C31 8(3) ?
 C32 C31 C36 C35 -14(2) ?
 C30 C31 C36 C35 176.9(16) ?
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 C9 C10 Br3 O5 48(4) . . . 2_656 ?
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 # END OF NADIA6 CIF

APPENDIX I: CHARACTERIZATION DATA OF COMPOUND 6.4

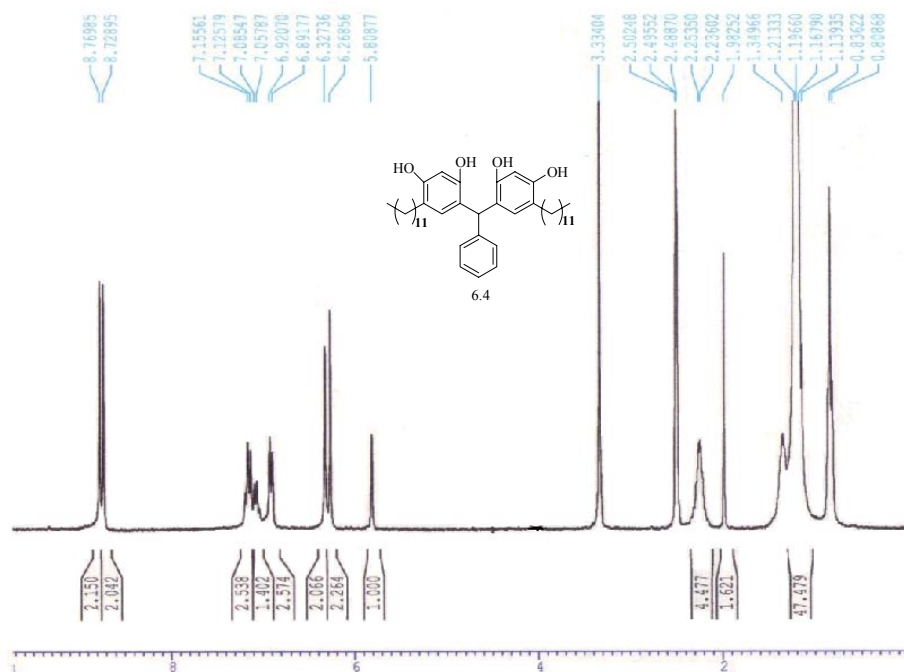


Figure I.1. ¹H NMR of compound 6.4

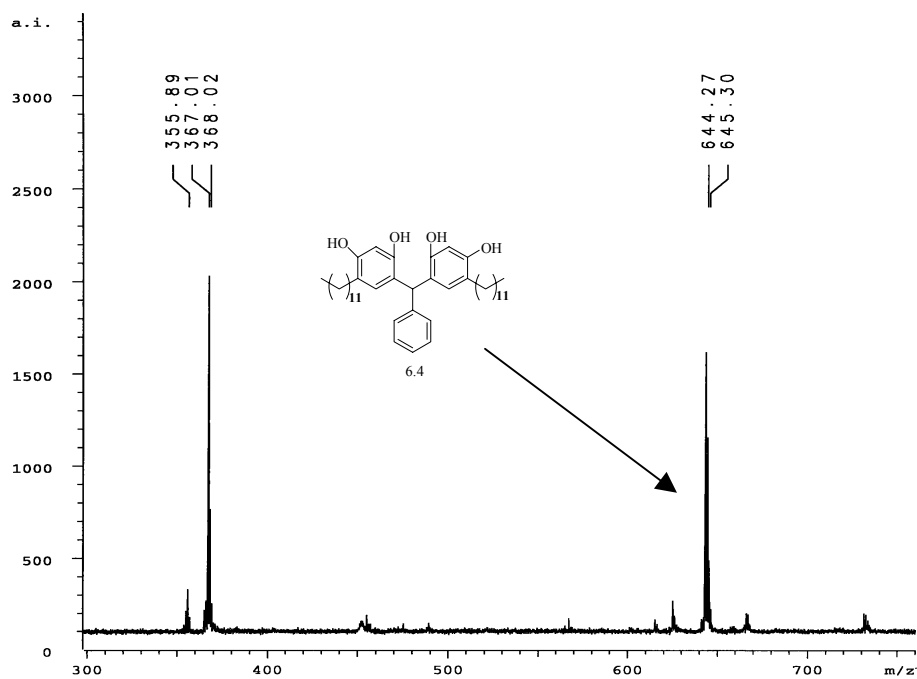


Figure I.2. MALDI MS of compound 6.4

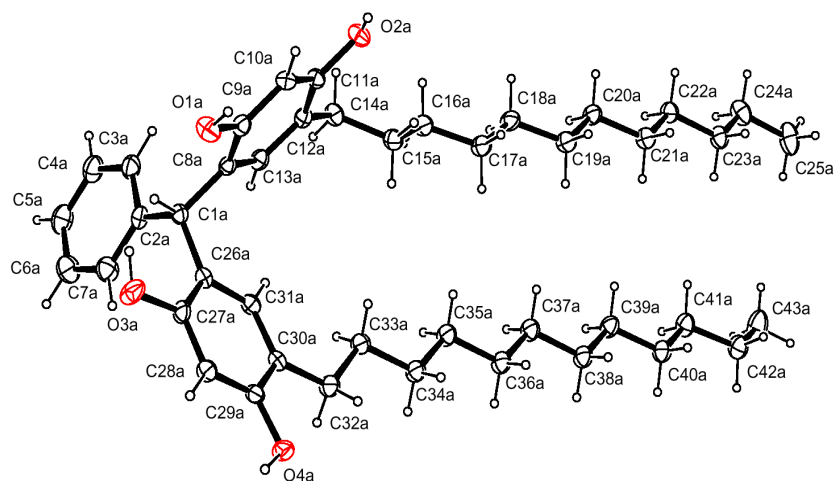


Figure I.3. Crystal structure of compound **6.4**

Table I.1. CIF data for compound **6.4**

CHEMICAL DATA

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_chemical_melting_point     ?
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_chemical_formula_weight    733.05

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_atom_type_scatter_dispersion_imag
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'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
'H' 'H' 0.0000 0.0000
'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
'O' 'O' 0.0106 0.0060

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CRYSTAL DATA

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loop_
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 '-x, -y, -z'
 'x-1/2, -y-1/2, z-1/2'

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 _cell_length_b 17.342(3)
 _cell_length_c 44.669(7)
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 _cell_angle_beta 94.740(6)
 _cell_angle_gamma 90
 _cell_volume 8751(2)
 _cell_formula_units_Z 8
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 _cell_measurement_reflns_used 10163
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EXPERIMENTAL DATA

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_diffn_measurement_device 'KappaCCD (with Oxford Cryostream)'
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_diffn_standards_interval_time ?
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_computing_publication_material 'SHELXL-97 (Sheldrick, 1997)'

REFINEMENT DATA

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Refinement of F^2 against ALL reflections. The weighted R-factor wR and goodness of fit S are based on F^2 , conventional R-factors R are based on F, with F set to zero for negative F^2 . The threshold expression of

$F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F , and R-factors based on ALL data will be even larger.

;

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ATOMIC COORDINATES AND THERMAL PARAMETERS

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  _atom_site_adp_type
  _atom_site_occupancy
  _atom_site_symmetry_multiplicity
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  _atom_site_disorder_group

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 O2A O 0.61918(14) 0.26055(10) 0.67820(4) 0.0313(5) Uani 1 1 d . . .
 H2OA H 0.6195 0.2926 0.6923 0.047 Uiso 1 1 calc R . .
 O3A O 1.28022(15) 0.11552(12) 0.72347(4) 0.0402(5) Uani 1 1 d . . .
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 O4A O 1.40694(14) 0.25698(10) 0.64123(4) 0.0302(5) Uani 1 1 d . . .
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 C1A C 1.0442(2) 0.08395(13) 0.69156(6) 0.0231(6) Uani 1 1 d . . .
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 C2A C 1.0317(2) -0.00041(14) 0.68204(6) 0.0259(6) Uani 1 1 d . . .
 C3A C 0.9250(2) -0.03961(15) 0.68316(6) 0.0336(7) Uani 1 1 d . . .
 H3A H 0.8569 -0.0121 0.6882 0.040 Uiso 1 1 calc R . .
 C4A C 0.9158(3) -0.11786(16) 0.67709(7) 0.0398(8) Uani 1 1 d . . .
 H4A H 0.8417 -0.1431 0.6777 0.048 Uiso 1 1 calc R . .
 C5A C 1.0134(3) -0.15887(17) 0.67027(7) 0.0437(8) Uani 1 1 d . . .
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 C6A C 1.1204(3) -0.12171(16) 0.66947(7) 0.0458(8) Uani 1 1 d . . .
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 C7A C 1.1297(2) -0.04255(15) 0.67501(7) 0.0367(7) Uani 1 1 d . . .
 H7A H 1.2037 -0.0174 0.6740 0.044 Uiso 1 1 calc R . .
 C8A C 0.9296(2) 0.12969(14) 0.68769(6) 0.0219(6) Uani 1 1 d . . .
 C9A C 0.8997(2) 0.17862(15) 0.71018(6) 0.0241(6) Uani 1 1 d . . .
 C10A C 0.7960(2) 0.22216(14) 0.70739(6) 0.0238(6) Uani 1 1 d . . .
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 C11A C 0.7224(2) 0.21746(14) 0.68121(6) 0.0245(6) Uani 1 1 d . . .
 C12A C 0.7473(2) 0.16952(14) 0.65768(6) 0.0234(6) Uani 1 1 d . . .
 C13A C 0.8515(2) 0.12636(14) 0.66170(6) 0.0245(6) Uani 1 1 d . . .
 H13A H 0.8705 0.0929 0.6460 0.029 Uiso 1 1 calc R . .
 C14A C 0.6669(2) 0.16455(15) 0.62928(6) 0.0283(7) Uani 1 1 d . . .
 H14A H 0.5847 0.1574 0.6347 0.034 Uiso 1 1 calc R . .
 H14B H 0.6886 0.1183 0.6180 0.034 Uiso 1 1 calc R . .
 C15A C 0.6702(2) 0.23491(15) 0.60856(6) 0.0285(7) Uani 1 1 d . . .
 H15A H 0.6621 0.2824 0.6205 0.034 Uiso 1 1 calc R . .
 H15B H 0.7479 0.2368 0.6000 0.034 Uiso 1 1 calc R . .
 C16A C 0.5725(2) 0.23297(15) 0.58312(6) 0.0296(7) Uani 1 1 d . . .
 H16A H 0.5833 0.1865 0.5708 0.036 Uiso 1 1 calc R . .
 H16B H 0.4955 0.2278 0.5919 0.036 Uiso 1 1 calc R . .
 C17A C 0.5673(2) 0.30304(16) 0.56272(6) 0.0309(7) Uani 1 1 d . . .
 H17A H 0.6365 0.3023 0.5506 0.037 Uiso 1 1 calc R . .
 H17B H 0.5726 0.3502 0.5752 0.037 Uiso 1 1 calc R . .
 C18A C 0.4546(2) 0.30612(16) 0.54180(6) 0.0314(7) Uani 1 1 d . . .
 H18A H 0.4473 0.2572 0.5304 0.038 Uiso 1 1 calc R . .
 H18B H 0.3862 0.3095 0.5541 0.038 Uiso 1 1 calc R . .
 C19A C 0.4474(2) 0.37247(16) 0.51960(6) 0.0318(7) Uani 1 1 d . . .
 H19A H 0.5139 0.3683 0.5066 0.038 Uiso 1 1 calc R . .

H19B H 0.4569 0.4216 0.5308 0.038 Uiso 1 1 calc R . .
C20A C 0.3317(2) 0.37478(15) 0.49982(6) 0.0301(7) Uani 1 1 d . . .
H20A H 0.2659 0.3828 0.5127 0.036 Uiso 1 1 calc R . .
H20B H 0.3195 0.3241 0.4898 0.036 Uiso 1 1 calc R . .
C21A C 0.3262(2) 0.43757(15) 0.47578(6) 0.0309(7) Uani 1 1 d . . .
H21A H 0.3375 0.4883 0.4858 0.037 Uiso 1 1 calc R . .
H21B H 0.3926 0.4299 0.4630 0.037 Uiso 1 1 calc R . .
C22A C 0.2110(2) 0.43917(16) 0.45578(6) 0.0310(7) Uani 1 1 d . . .
H22A H 0.1971 0.3874 0.4468 0.037 Uiso 1 1 calc R . .
H22B H 0.1452 0.4502 0.4684 0.037 Uiso 1 1 calc R . .
C23A C 0.2084(2) 0.49802(16) 0.43070(6) 0.0342(7) Uani 1 1 d . . .
H23A H 0.2752 0.4875 0.4183 0.041 Uiso 1 1 calc R . .
H23B H 0.2209 0.5499 0.4397 0.041 Uiso 1 1 calc R . .
C24A C 0.0941(3) 0.49880(17) 0.41030(7) 0.0414(8) Uani 1 1 d . . .
H24A H 0.0274 0.5104 0.4225 0.050 Uiso 1 1 calc R . .
H24B H 0.0807 0.4468 0.4016 0.050 Uiso 1 1 calc R . .
C25A C 0.0941(3) 0.55727(17) 0.38491(7) 0.0538(9) Uani 1 1 d . . .
H25A H 0.1068 0.6091 0.3933 0.081 Uiso 1 1 calc R . .
H25B H 0.0178 0.5555 0.3729 0.081 Uiso 1 1 calc R . .
H25C H 0.1578 0.5449 0.3721 0.081 Uiso 1 1 calc R . .
C26A C 1.1451(2) 0.12644(14) 0.67797(6) 0.0223(6) Uani 1 1 d . . .
C27A C 1.2524(2) 0.14134(15) 0.69446(6) 0.0261(6) Uani 1 1 d . . .
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C29A C 1.3235(2) 0.21199(14) 0.65356(6) 0.0240(6) Uani 1 1 d . . .
C30A C 1.2179(2) 0.19876(14) 0.63569(6) 0.0232(6) Uani 1 1 d . . .
C31A C 1.1322(2) 0.15586(14) 0.64882(6) 0.0240(6) Uani 1 1 d . . .
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C32A C 1.2012(2) 0.23600(16) 0.60512(6) 0.0299(7) Uani 1 1 d . . .
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H32B H 1.2316 0.2894 0.6070 0.036 Uiso 1 1 calc R . .
C33A C 1.0772(2) 0.23951(15) 0.58974(6) 0.0291(7) Uani 1 1 d . . .
H33A H 1.0221 0.2589 0.6041 0.035 Uiso 1 1 calc R . .
H33B H 1.0515 0.1870 0.5835 0.035 Uiso 1 1 calc R . .
C34A C 1.0720(2) 0.29200(16) 0.56234(6) 0.0302(7) Uani 1 1 d . . .
H34A H 1.1319 0.2741 0.5490 0.036 Uiso 1 1 calc R . .
H34B H 1.0947 0.3447 0.5691 0.036 Uiso 1 1 calc R . .
C35A C 0.9526(2) 0.29625(15) 0.54408(6) 0.0307(7) Uani 1 1 d . . .
H35A H 0.8913 0.3114 0.5575 0.037 Uiso 1 1 calc R . .
H35B H 0.9318 0.2444 0.5360 0.037 Uiso 1 1 calc R . .
C36A C 0.9512(2) 0.35340(16) 0.51806(6) 0.0307(7) Uani 1 1 d . . .
H36A H 0.9695 0.4054 0.5263 0.037 Uiso 1 1 calc R . .
H36B H 1.0148 0.3392 0.5052 0.037 Uiso 1 1 calc R . .
C37A C 0.8346(2) 0.35735(16) 0.49854(6) 0.0313(7) Uani 1 1 d . . .
H37A H 0.8169 0.3057 0.4899 0.038 Uiso 1 1 calc R . .
H37B H 0.7705 0.3707 0.5114 0.038 Uiso 1 1 calc R . .

C38A C 0.8346(2) 0.41563(15) 0.47319(6) 0.0323(7) Uani 1 1 d . . .
 H38A H 0.9006 0.4033 0.4608 0.039 Uiso 1 1 calc R . .
 H38B H 0.8500 0.4674 0.4820 0.039 Uiso 1 1 calc R . .
 C39A C 0.7200(2) 0.41845(16) 0.45286(6) 0.0327(7) Uani 1 1 d . . .
 H39A H 0.7066 0.3673 0.4433 0.039 Uiso 1 1 calc R . .
 H39B H 0.6535 0.4284 0.4654 0.039 Uiso 1 1 calc R . .
 C40A C 0.7182(2) 0.47926(16) 0.42842(6) 0.0342(7) Uani 1 1 d . . .
 H40A H 0.7264 0.5306 0.4380 0.041 Uiso 1 1 calc R . .
 H40B H 0.7879 0.4714 0.4168 0.041 Uiso 1 1 calc R . .
 C41A C 0.6080(2) 0.47927(16) 0.40686(6) 0.0348(7) Uani 1 1 d . . .
 H41A H 0.5378 0.4834 0.4185 0.042 Uiso 1 1 calc R . .
 H41B H 0.6030 0.4295 0.3960 0.042 Uiso 1 1 calc R . .
 C42A C 0.6047(2) 0.54444(16) 0.38402(7) 0.0376(7) Uani 1 1 d . . .
 H42A H 0.6003 0.5941 0.3948 0.045 Uiso 1 1 calc R . .
 H42B H 0.6796 0.5440 0.3741 0.045 Uiso 1 1 calc R . .
 C43A C 0.5021(3) 0.54009(19) 0.36007(8) 0.0562(10) Uani 1 1 d . . .
 H43A H 0.5052 0.4910 0.3493 0.084 Uiso 1 1 calc R . .
 H43B H 0.5074 0.5828 0.3459 0.084 Uiso 1 1 calc R . .
 H43C H 0.4273 0.5436 0.3695 0.084 Uiso 1 1 calc R . .
 O1B O 1.03336(16) 0.69620(10) 0.74779(4) 0.0339(5) Uani 1 1 d . . .
 H1OB H 1.0861 0.6624 0.7509 0.051 Uiso 1 1 calc R . .
 O2B O 0.67889(14) 0.74904(10) 0.68756(4) 0.0290(5) Uani 1 1 d . . .
 H2OB H 0.6634 0.7700 0.7037 0.044 Uiso 1 1 calc R . .
 O3B O 1.34670(15) 0.57935(11) 0.72937(4) 0.0350(5) Uani 1 1 d . . .
 H3OB H 1.4199 0.5716 0.7322 0.053 Uiso 1 1 calc R . .
 O4B O 1.46920(14) 0.74767(11) 0.65167(4) 0.0330(5) Uani 1 1 d . . .
 H4OB H 1.5348 0.7432 0.6617 0.050 Uiso 1 1 calc R . .
 C1B C 1.1102(2) 0.57913(14) 0.70461(6) 0.0238(6) Uani 1 1 d . . .
 H1B H 1.1345 0.5782 0.7266 0.029 Uiso 1 1 calc R . .
 C2B C 1.0961(2) 0.49469(14) 0.69476(6) 0.0259(6) Uani 1 1 d . . .
 C3B C 0.9990(2) 0.45232(15) 0.70239(7) 0.0368(7) Uani 1 1 d . . .
 H3B H 0.9408 0.4764 0.7133 0.044 Uiso 1 1 calc R . .
 C4B C 0.9857(3) 0.37574(16) 0.69434(7) 0.0437(8) Uani 1 1 d . . .
 H4B H 0.9180 0.3479 0.6994 0.052 Uiso 1 1 calc R . .
 C5B C 1.0702(3) 0.33998(17) 0.67906(7) 0.0432(8) Uani 1 1 d . . .
 H5B H 1.0611 0.2872 0.6736 0.052 Uiso 1 1 calc R . .
 C6B C 1.1681(3) 0.38014(16) 0.67154(7) 0.0413(8) Uani 1 1 d . . .
 H6B H 1.2270 0.3551 0.6612 0.050 Uiso 1 1 calc R . .
 C7B C 1.1804(2) 0.45767(15) 0.67921(6) 0.0341(7) Uani 1 1 d . . .
 H7B H 1.2474 0.4855 0.6737 0.041 Uiso 1 1 calc R . .
 C8B C 0.9935(2) 0.62407(14) 0.70088(6) 0.0216(6) Uani 1 1 d . . .
 C9B C 0.9643(2) 0.67871(14) 0.72195(6) 0.0231(6) Uani 1 1 d . . .
 C10B C 0.8592(2) 0.72017(14) 0.71760(6) 0.0246(6) Uani 1 1 d . . .
 H10B H 0.8391 0.7569 0.7321 0.030 Uiso 1 1 calc R . .
 C11B C 0.7843(2) 0.70771(14) 0.69217(6) 0.0235(6) Uani 1 1 d . . .
 C12B C 0.8091(2) 0.65487(14) 0.67033(6) 0.0227(6) Uani 1 1 d . . .

C13B C 0.9147(2) 0.61399(14) 0.67549(6) 0.0235(6) Uani 1 1 d . . .
 H13B H 0.9341 0.5772 0.6609 0.028 Uiso 1 1 calc R . .
 C14B C 0.7275(2) 0.64282(15) 0.64239(6) 0.0275(7) Uani 1 1 d . . .
 H14C H 0.6456 0.6374 0.6482 0.033 Uiso 1 1 calc R . .
 H14D H 0.7491 0.5939 0.6328 0.033 Uiso 1 1 calc R . .
 C15B C 0.7307(2) 0.70778(16) 0.61939(6) 0.0312(7) Uani 1 1 d . . .
 H15C H 0.7242 0.7579 0.6298 0.037 Uiso 1 1 calc R . .
 H15D H 0.8079 0.7067 0.6105 0.037 Uiso 1 1 calc R . .
 C16B C 0.6318(2) 0.70178(15) 0.59427(6) 0.0312(7) Uani 1 1 d . . .
 H16C H 0.6419 0.6532 0.5831 0.037 Uiso 1 1 calc R . .
 H16D H 0.5551 0.6988 0.6033 0.037 Uiso 1 1 calc R . .
 C17B C 0.6273(2) 0.76852(16) 0.57226(6) 0.0369(7) Uani 1 1 d . . .
 H17C H 0.6954 0.7645 0.5598 0.044 Uiso 1 1 calc R . .
 H17D H 0.6356 0.8175 0.5836 0.044 Uiso 1 1 calc R . .
 C18B C 0.5132(2) 0.77102(16) 0.55168(6) 0.0330(7) Uani 1 1 d . . .
 H18C H 0.5055 0.7219 0.5404 0.040 Uiso 1 1 calc R . .
 H18D H 0.4455 0.7745 0.5643 0.040 Uiso 1 1 calc R . .
 C19B C 0.5051(2) 0.83733(16) 0.52939(6) 0.0358(7) Uani 1 1 d . . .
 H19C H 0.5693 0.8320 0.5158 0.043 Uiso 1 1 calc R . .
 H19D H 0.5178 0.8864 0.5405 0.043 Uiso 1 1 calc R . .
 C20B C 0.3872(2) 0.84134(16) 0.51057(6) 0.0340(7) Uani 1 1 d . . .
 H20C H 0.3739 0.7918 0.4998 0.041 Uiso 1 1 calc R . .
 H20D H 0.3232 0.8475 0.5242 0.041 Uiso 1 1 calc R . .
 C21B C 0.3782(2) 0.90606(16) 0.48786(6) 0.0342(7) Uani 1 1 d . . .
 H21C H 0.4428 0.9003 0.4744 0.041 Uiso 1 1 calc R . .
 H21D H 0.3905 0.9557 0.4986 0.041 Uiso 1 1 calc R . .
 C22B C 0.2610(2) 0.90947(16) 0.46880(6) 0.0338(7) Uani 1 1 d . . .
 H22C H 0.2469 0.8590 0.4588 0.041 Uiso 1 1 calc R . .
 H22D H 0.1968 0.9178 0.4822 0.041 Uiso 1 1 calc R . .
 C23B C 0.2538(2) 0.97197(16) 0.44504(7) 0.0364(7) Uani 1 1 d . . .
 H23C H 0.3189 0.9644 0.4319 0.044 Uiso 1 1 calc R . .
 H23D H 0.2660 1.0226 0.4550 0.044 Uiso 1 1 calc R . .
 C24B C 0.1366(2) 0.97370(17) 0.42560(7) 0.0426(8) Uani 1 1 d . . .
 H24C H 0.1245 0.9232 0.4155 0.051 Uiso 1 1 calc R . .
 H24D H 0.0713 0.9811 0.4387 0.051 Uiso 1 1 calc R . .
 C25B C 0.1304(3) 1.03685(18) 0.40202(7) 0.0525(9) Uani 1 1 d . . .
 H25D H 0.1441 1.0870 0.4118 0.079 Uiso 1 1 calc R . .
 H25E H 0.0520 1.0365 0.3910 0.079 Uiso 1 1 calc R . .
 H25F H 0.1910 1.0278 0.3880 0.079 Uiso 1 1 calc R . .
 C26B C 1.2079(2) 0.62167(14) 0.68997(6) 0.0227(6) Uani 1 1 d . . .
 C27B C 1.3227(2) 0.62215(15) 0.70315(6) 0.0267(6) Uani 1 1 d . . .
 C28B C 1.4118(2) 0.66321(15) 0.69083(6) 0.0277(7) Uani 1 1 d . . .
 H28B H 1.4896 0.6639 0.7005 0.033 Uiso 1 1 calc R . .
 C29B C 1.3865(2) 0.70320(15) 0.66424(6) 0.0264(6) Uani 1 1 d . . .
 C30B C 1.2747(2) 0.69969(14) 0.64860(6) 0.0255(6) Uani 1 1 d . . .
 C31B C 1.1880(2) 0.65956(14) 0.66243(6) 0.0245(6) Uani 1 1 d . . .

H31B H 1.1106 0.6578 0.6525 0.029 Uiso 1 1 calc R . .
 C32B C 1.2547(2) 0.73995(16) 0.61882(6) 0.0302(7) Uani 1 1 d . . .
 H32C H 1.3131 0.7197 0.6055 0.036 Uiso 1 1 calc R . .
 H32D H 1.2723 0.7954 0.6221 0.036 Uiso 1 1 calc R . .
 C33B C 1.1320(2) 0.73346(16) 0.60211(6) 0.0309(7) Uani 1 1 d . . .
 H33C H 1.1163 0.6790 0.5964 0.037 Uiso 1 1 calc R . .
 H33D H 1.0714 0.7498 0.6155 0.037 Uiso 1 1 calc R . .
 C34B C 1.1230(2) 0.78339(16) 0.57411(6) 0.0321(7) Uani 1 1 d . . .
 H34C H 1.1851 0.7670 0.5611 0.039 Uiso 1 1 calc R . .
 H34D H 1.1399 0.8375 0.5802 0.039 Uiso 1 1 calc R . .
 C35B C 1.0038(2) 0.78093(15) 0.55568(6) 0.0304(7) Uani 1 1 d . . .
 H35C H 0.9896 0.7280 0.5479 0.037 Uiso 1 1 calc R . .
 H35D H 0.9404 0.7934 0.5689 0.037 Uiso 1 1 calc R . .
 C36B C 0.9972(2) 0.83676(16) 0.52961(6) 0.0333(7) Uani 1 1 d . . .
 H36C H 1.0585 0.8223 0.5161 0.040 Uiso 1 1 calc R . .
 H36D H 1.0168 0.8890 0.5375 0.040 Uiso 1 1 calc R . .
 C37B C 0.8790(2) 0.84048(16) 0.51132(6) 0.0317(7) Uani 1 1 d . . .
 H37C H 0.8170 0.8540 0.5248 0.038 Uiso 1 1 calc R . .
 H37D H 0.8600 0.7888 0.5028 0.038 Uiso 1 1 calc R . .
 C38B C 0.8753(2) 0.89868(16) 0.48579(6) 0.0343(7) Uani 1 1 d . . .
 H38C H 0.8981 0.9498 0.4943 0.041 Uiso 1 1 calc R . .
 H38D H 0.9352 0.8838 0.4719 0.041 Uiso 1 1 calc R . .
 C39B C 0.7566(2) 0.90616(16) 0.46790(7) 0.0359(7) Uani 1 1 d . . .
 H39C H 0.6962 0.9195 0.4818 0.043 Uiso 1 1 calc R . .
 H39D H 0.7348 0.8554 0.4589 0.043 Uiso 1 1 calc R . .
 C40B C 0.7525(2) 0.96587(17) 0.44311(7) 0.0409(8) Uani 1 1 d . . .
 H40C H 0.8111 0.9516 0.4288 0.049 Uiso 1 1 calc R . .
 H40D H 0.7767 1.0163 0.4520 0.049 Uiso 1 1 calc R . .
 C41B C 0.6322(3) 0.97497(18) 0.42579(7) 0.0494(9) Uani 1 1 d . . .
 H41C H 0.5719 0.9835 0.4403 0.059 Uiso 1 1 calc R . .
 H41D H 0.6120 0.9264 0.4149 0.059 Uiso 1 1 calc R . .
 C42B C 0.6262(3) 1.0414(2) 0.40326(9) 0.0655(11) Uani 1 1 d . . .
 C43B C 0.5123(5) 1.0547(3) 0.38670(14) 0.0581(13) Uiso 0.597(5) 1 d P . .
 C43C C 0.6891(8) 1.0275(5) 0.3806(2) 0.0581(13) Uiso 0.403(5) 1 d P . .
 O1S O 0.86935(18) 0.87749(13) 0.77957(5) 0.0578(7) Uani 1 1 d . . .
 O2S O 0.93988(19) 0.99400(13) 0.77051(6) 0.0727(8) Uani 1 1 d . . .
 O3S O 0.54826(16) 0.81327(11) 0.72999(4) 0.0370(5) Uani 1 1 d . . .
 O4S O 0.4501(2) 0.91270(13) 0.70803(6) 0.0715(8) Uani 1 1 d . . .
 C1S C 0.9500(3) 0.9184(2) 0.77131(8) 0.0470(9) Uani 1 1 d . . .
 C2S C 1.0627(3) 0.88992(17) 0.76146(8) 0.0496(9) Uani 1 1 d . . .
 H2S1 H 1.0643 0.8335 0.7626 0.074 Uiso 1 1 calc R . .
 H2S2 H 1.1285 0.9110 0.7745 0.074 Uiso 1 1 calc R . .
 H2S3 H 1.0704 0.9063 0.7407 0.074 Uiso 1 1 calc R . .
 C3S C 0.8280(3) 1.0288(2) 0.77877(12) 0.0799(15) Uani 1 1 d . . .
 H3S1 H 0.7954 0.9976 0.7947 0.096 Uiso 1 1 calc R . .
 H3S2 H 0.8434 1.0814 0.7867 0.096 Uiso 1 1 calc R . .

C4S C 0.7422(4) 1.0322(2) 0.75261(11) 0.0947(17) Uani 1 1 d . . .
 H4S1 H 0.6688 1.0559 0.7583 0.142 Uiso 1 1 calc R . .
 H4S2 H 0.7257 0.9800 0.7451 0.142 Uiso 1 1 calc R . .
 H4S3 H 0.7746 1.0633 0.7369 0.142 Uiso 1 1 calc R . .
 C5S C 0.4570(3) 0.85085(19) 0.72517(7) 0.0442(8) Uani 1 1 d . . .
 C6S C 0.3423(3) 0.8315(2) 0.73709(8) 0.0636(11) Uani 1 1 d . . .
 H6S1 H 0.3532 0.7880 0.7511 0.095 Uiso 1 1 d R . .
 H6S2 H 0.2846 0.8174 0.7204 0.095 Uiso 1 1 d R . .
 H6S3 H 0.3132 0.8763 0.7477 0.095 Uiso 1 1 d R . .
 C7S C 0.5544(4) 0.9358(2) 0.69393(13) 0.1007(18) Uani 1 1 d . . .
 H7S1 H 0.5602 0.9076 0.6748 0.121 Uiso 1 1 calc R . .
 H7S2 H 0.6267 0.9257 0.7073 0.121 Uiso 1 1 calc R . .
 C8S C 0.5385(4) 1.0220(2) 0.68818(15) 0.136(2) Uani 1 1 d . . .
 H8S1 H 0.6065 1.0419 0.6784 0.204 Uiso 1 1 calc R . .
 H8S2 H 0.5326 1.0488 0.7073 0.204 Uiso 1 1 calc R . .
 H8S3 H 0.4659 1.0307 0.6751 0.204 Uiso 1 1 calc R . .

MOLECULAR GEOMETRY

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 O1A 0.0305(10) 0.0440(13) 0.0234(12) -0.0069(10) -0.0043(9) 0.0070(9)
 O2A 0.0228(10) 0.0368(12) 0.0337(13) -0.0018(9) -0.0019(8) 0.0047(8)
 O3A 0.0279(11) 0.0624(14) 0.0291(13) 0.0186(11) -0.0051(9) -0.0115(10)
 O4A 0.0200(10) 0.0418(11) 0.0283(12) 0.0090(10) -0.0013(8) -0.0038(8)
 C1A 0.0212(14) 0.0240(15) 0.0236(16) 0.0039(13) -0.0007(11) 0.0016(11)
 C2A 0.0301(15) 0.0229(15) 0.0241(17) 0.0047(13) -0.0021(12) -0.0010(12)
 C3A 0.0348(16) 0.0254(16) 0.040(2) 0.0076(14) 0.0015(14) -0.0013(12)
 C4A 0.0429(18) 0.0309(18) 0.045(2) 0.0074(16) -0.0026(15) -0.0068(14)
 C5A 0.058(2) 0.0248(16) 0.048(2) 0.0022(16) 0.0011(17) -0.0055(15)
 C6A 0.053(2) 0.0311(18) 0.054(2) -0.0045(17) 0.0096(17) 0.0085(15)
 C7A 0.0381(17) 0.0299(17) 0.042(2) -0.0021(15) 0.0031(14) 0.0004(13)
 C8A 0.0198(13) 0.0235(15) 0.0222(16) 0.0038(13) 0.0002(12) -0.0038(10)
 C9A 0.0224(14) 0.0284(15) 0.0209(17) 0.0041(13) -0.0028(12) -0.0035(11)
 C10A 0.0205(14) 0.0266(15) 0.0247(17) -0.0020(13) 0.0032(12) -0.0007(11)
 C11A 0.0146(13) 0.0270(15) 0.0312(18) 0.0058(14) -0.0018(12) -0.0001(11)
 C12A 0.0233(14) 0.0237(15) 0.0227(16) 0.0026(13) -0.0010(12) -0.0034(11)
 C13A 0.0263(14) 0.0227(15) 0.0243(17) 0.0006(13) 0.0009(12) -0.0041(11)
 C14A 0.0271(15) 0.0287(16) 0.0282(17) -0.0023(14) -0.0034(12) 0.0017(11)

C15A 0.0252(15) 0.0336(16) 0.0261(17) 0.0005(14) -0.0010(12) 0.0017(12)
 C16A 0.0263(15) 0.0353(17) 0.0267(17) 0.0012(14) -0.0012(12) -0.0010(12)
 C17A 0.0271(15) 0.0412(17) 0.0239(17) 0.0048(14) -0.0012(12) 0.0002(12)
 C18A 0.0285(15) 0.0403(17) 0.0253(17) 0.0067(14) 0.0018(12) 0.0000(12)
 C19A 0.0271(15) 0.0391(17) 0.0286(18) 0.0030(14) -0.0014(13) -0.0007(12)
 C20A 0.0281(15) 0.0347(17) 0.0271(17) 0.0043(14) -0.0001(12) -0.0014(12)
 C21A 0.0286(15) 0.0372(17) 0.0258(17) 0.0010(14) -0.0039(13) -0.0004(12)
 C22A 0.0294(15) 0.0362(17) 0.0268(18) 0.0047(14) -0.0023(13) 0.0043(12)
 C23A 0.0382(17) 0.0345(17) 0.0290(18) 0.0027(14) -0.0025(13) 0.0046(13)
 C24A 0.0443(18) 0.047(2) 0.0308(19) -0.0012(16) -0.0090(15) 0.0122(14)
 C25A 0.077(2) 0.044(2) 0.036(2) -0.0005(18) -0.0189(18) 0.0173(17)
 C26A 0.0211(14) 0.0210(14) 0.0242(17) -0.0002(13) -0.0012(12) 0.0027(10)
 C27A 0.0255(15) 0.0291(16) 0.0228(17) 0.0070(13) -0.0030(12) 0.0009(11)
 C28A 0.0182(14) 0.0344(16) 0.0241(17) 0.0042(14) -0.0065(12) -0.0024(11)
 C29A 0.0184(14) 0.0246(15) 0.0293(18) -0.0001(13) 0.0035(12) 0.0022(11)
 C30A 0.0203(14) 0.0239(15) 0.0252(17) -0.0001(13) 0.0001(12) 0.0042(11)
 C31A 0.0181(13) 0.0275(15) 0.0255(17) -0.0024(13) -0.0038(11) -0.0003(11)
 C32A 0.0275(15) 0.0379(17) 0.0240(17) 0.0042(14) 0.0006(12) 0.0002(12)
 C33A 0.0247(15) 0.0348(16) 0.0273(17) 0.0050(14) 0.0000(12) 0.0005(12)
 C34A 0.0268(15) 0.0353(16) 0.0278(18) 0.0061(14) -0.0015(12) -0.0020(12)
 C35A 0.0265(15) 0.0372(17) 0.0272(17) 0.0075(14) -0.0044(12) -0.0028(12)
 C36A 0.0316(16) 0.0360(17) 0.0240(17) 0.0051(14) -0.0008(13) -0.0001(12)
 C37A 0.0306(16) 0.0353(17) 0.0272(18) 0.0054(14) -0.0024(13) -0.0004(12)
 C38A 0.0316(16) 0.0362(17) 0.0288(18) 0.0061(14) -0.0002(13) -0.0004(13)
 C39A 0.0340(16) 0.0355(17) 0.0280(18) 0.0069(14) -0.0007(13) -0.0031(13)
 C40A 0.0337(16) 0.0378(17) 0.0309(18) 0.0089(15) 0.0006(13) 0.0024(13)
 C41A 0.0356(16) 0.0360(17) 0.0314(18) 0.0060(15) -0.0066(14) -0.0010(13)
 C42A 0.0403(17) 0.0393(18) 0.0324(19) 0.0045(15) -0.0027(14) 0.0004(13)
 C43A 0.067(2) 0.047(2) 0.050(2) 0.0159(18) -0.0232(18) -0.0085(17)
 O1B 0.0344(11) 0.0354(12) 0.0298(12) -0.0096(10) -0.0104(9) 0.0105(9)
 O2B 0.0214(10) 0.0341(11) 0.0313(12) -0.0024(10) 0.0006(8) 0.0060(8)
 O3B 0.0241(10) 0.0518(13) 0.0287(12) 0.0127(10) -0.0004(9) 0.0054(9)
 O4B 0.0209(10) 0.0429(12) 0.0349(13) 0.0081(10) -0.0004(9) -0.0036(9)
 C1B 0.0245(14) 0.0269(15) 0.0197(16) -0.0027(13) 0.0000(11) 0.0042(11)
 C2B 0.0302(15) 0.0220(15) 0.0248(17) 0.0011(13) -0.0029(12) 0.0040(11)
 C3B 0.0407(18) 0.0289(17) 0.042(2) -0.0001(15) 0.0119(15) 0.0001(13)
 C4B 0.054(2) 0.0275(17) 0.051(2) 0.0055(16) 0.0135(17) -0.0064(14)
 C5B 0.066(2) 0.0215(16) 0.042(2) 0.0009(15) 0.0095(17) 0.0014(15)
 C6B 0.052(2) 0.0287(17) 0.044(2) -0.0085(16) 0.0092(16) 0.0067(14)
 C7B 0.0380(17) 0.0305(17) 0.0345(19) 0.0002(15) 0.0071(14) 0.0056(13)
 C8B 0.0202(13) 0.0200(14) 0.0246(16) 0.0004(13) 0.0024(12) -0.0012(10)
 C9B 0.0252(14) 0.0233(15) 0.0203(16) 0.0008(13) -0.0003(12) -0.0023(11)
 C10B 0.0262(14) 0.0226(14) 0.0254(17) -0.0045(13) 0.0039(12) 0.0027(11)
 C11B 0.0178(13) 0.0245(15) 0.0281(17) 0.0050(13) 0.0023(12) 0.0008(11)
 C12B 0.0235(14) 0.0205(14) 0.0241(16) 0.0015(13) 0.0027(12) -0.0034(11)
 C13B 0.0253(14) 0.0231(14) 0.0222(16) -0.0023(13) 0.0017(12) -0.0009(11)

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_geom_special_details

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All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken

into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

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 C13B C12B C14B C15B -105.2(3) ?
 C12B C14B C15B C16B -169.2(2) ?
 C14B C15B C16B C17B 175.9(2) ?
 C15B C16B C17B C18B -167.1(2) ?
 C16B C17B C18B C19B 179.7(2) ?
 C17B C18B C19B C20B -176.3(2) ?
 C18B C19B C20B C21B -178.9(3) ?
 C19B C20B C21B C22B 179.3(2) ?
 C20B C21B C22B C23B -177.3(3) ?
 C21B C22B C23B C24B 178.8(2) ?
 C22B C23B C24B C25B 179.7(3) ?
 C8B C1B C26B C27B 142.1(2) ?
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 C8B C1B C26B C31B -40.1(3) ?
 C2B C1B C26B C31B 88.2(3) ?
 C31B C26B C27B C28B 4.8(4) ?
 C1B C26B C27B C28B -177.3(2) ?
 C31B C26B C27B O3B -174.8(2) ?
 C1B C26B C27B O3B 3.1(4) ?
 C26B C27B C28B C29B -1.7(4) ?
 O3B C27B C28B C29B 177.9(2) ?
 C27B C28B C29B O4B 176.9(2) ?
 C27B C28B C29B C30B -3.6(4) ?
 O4B C29B C30B C31B -175.2(2) ?
 C28B C29B C30B C31B 5.4(4) ?
 O4B C29B C30B C32B 3.6(4) ?
 C28B C29B C30B C32B -175.9(2) ?
 C29B C30B C31B C26B -2.0(4) ?
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 C27B C26B C31B C30B -2.9(4) ?
 C1B C26B C31B C30B 179.2(2) ?
 C31B C30B C32B C33B -2.6(4) ?
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 C39B C40B C41B C42B 173.6(3) ?
 C40B C41B C42B C43C 69.3(6) ?
 C40B C41B C42B C43B -178.0(4) ?
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 C3S O2S C1S C2S 177.6(3) ?
 C1S O2S C3S C4S -86.5(5) ?
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 O2A H2OA O1S 0.84 1.93 2.766(3) 171.1 2_646
 O3A H3OA O3B 0.84 2.00 2.721(3) 144.0 2_746
 O4A H4OA O2A 0.84 1.97 2.804(2) 174.9 1_655
 O1B H1OB O3A 0.84 2.00 2.761(2) 151.0 2_756
 O2B H2OB O3S 0.84 1.97 2.737(3) 150.6 .
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APPENDIX J: CHARACTERIZATION DATA FOR COMPOUND 6.5

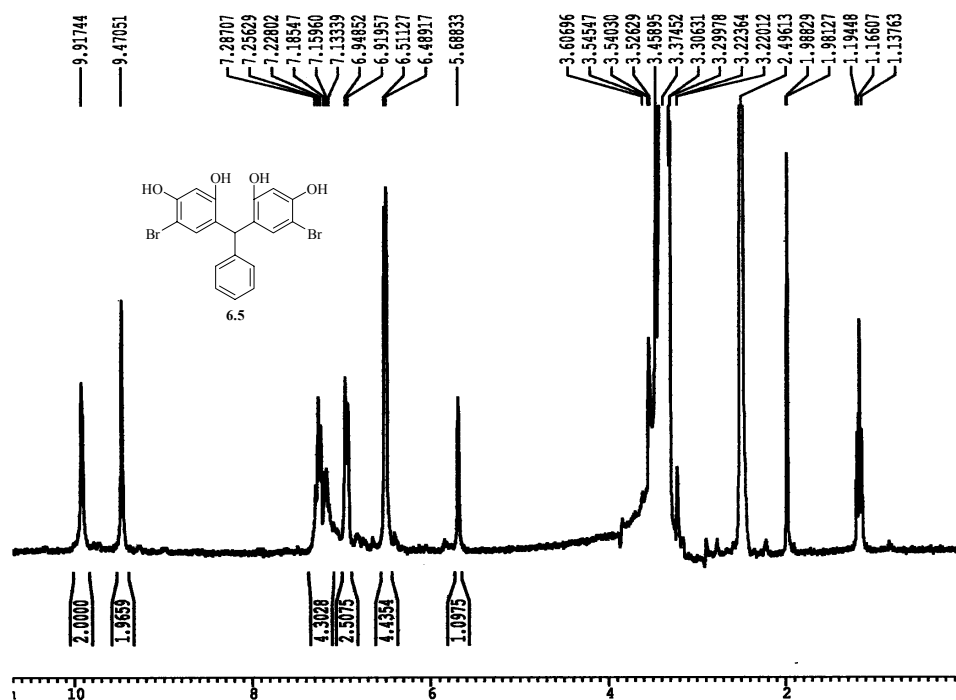


Figure J.1. ¹H NMR of compound 6.5

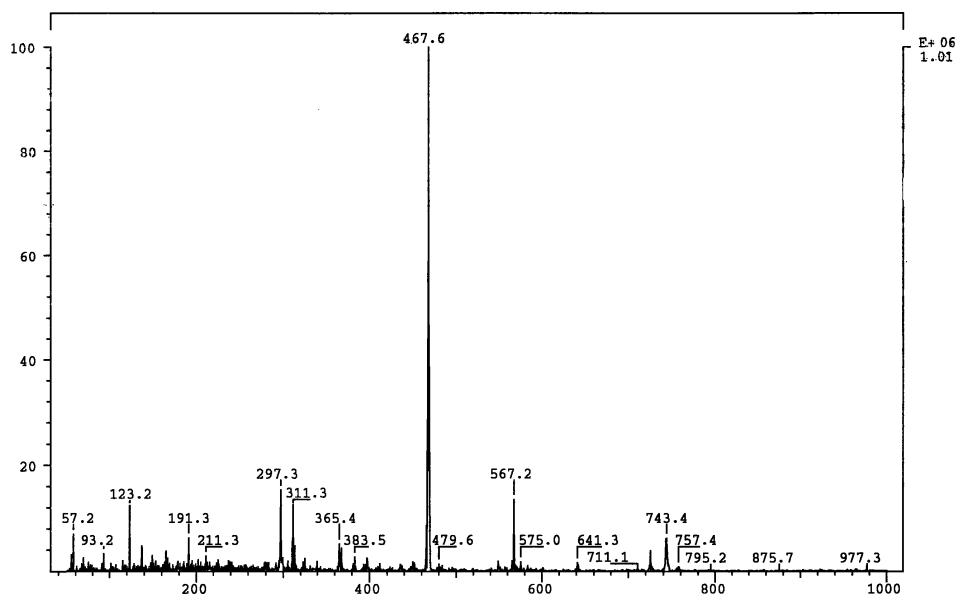


Figure J.2. FAB-MS of compound 6.5

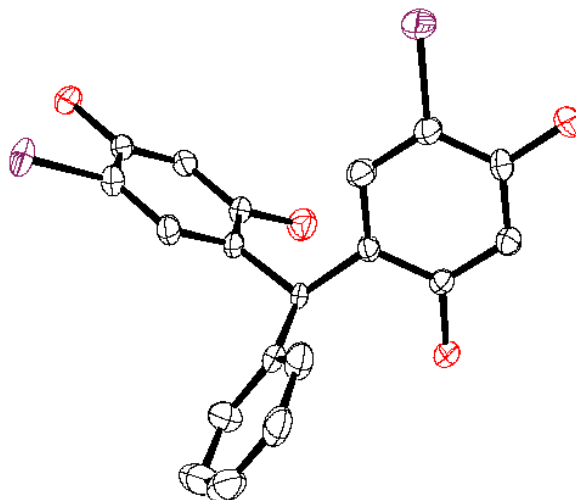


Figure J.3. Crystal structure of compound **6.5**

Table J.1. CIF datat for compound **6.5**

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'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'

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 'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
 'Br' 'Br' -0.2901 2.4595
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 'x-1/2, -y-1/2, z-1/2'

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_cell_length_c	20.787(2)
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_cell_angle_beta	101.381(4)
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_exptl_crystal_size_min	0.17
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_exptl_crystal_F_000	2608
_exptl_absorpt_coefficient_mu	3.133
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_exptl_special_details

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_refine_ls_weighting_scheme calc

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_refine_ls_hydrogen_treatment none

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ATOMIC COORDINATES AND THERMAL PARAMETERS

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_atom_site_fract_z
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 C20 C 0.3530(3) 0.2233(2) 0.4407(2) 0.0242(8) Uani 1 1 d . . .
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 C20 0.0155(18) 0.033(2) 0.024(2) 0.0001(17) 0.0047(16) 0.0013(16)
 C22 0.0097(16) 0.033(2) 0.0209(19) -0.0003(16) 0.0034(14) 0.0032(15)
 C23 0.028(2) 0.029(2) 0.026(2) -0.0035(18) 0.0085(18) 0.0003(18)
 C25 0.0170(19) 0.030(2) 0.025(2) -0.0007(17) 0.0076(16) 0.0044(16)
 C26 0.017(2) 0.034(2) 0.035(2) -0.0025(19) 0.0065(18) 0.0064(17)
 C27 0.0170(19) 0.035(2) 0.027(2) -0.0034(18) 0.0056(17) -0.0016(16)
 C28 0.0190(19) 0.023(2) 0.0227(19) -0.0026(16) 0.0032(16) -0.0006(15)
 C29 0.0162(18) 0.0210(19) 0.024(2) 0.0006(16) 0.0031(15) 0.0015(15)
 C30 0.021(2) 0.029(2) 0.029(2) 0.0000(18) 0.0078(17) 0.0014(17)
 C31 0.0174(19) 0.037(2) 0.025(2) 0.0077(18) 0.0058(16) 0.0048(17)
 C32 0.0155(18) 0.030(2) 0.024(2) 0.0010(17) 0.0002(16) 0.0031(16)
 C33 0.0193(18) 0.0209(19) 0.0207(19) -0.0014(15) 0.0056(15) 0.0016(15)
 C34 0.0185(19) 0.0222(19) 0.0229(19) -0.0007(16) 0.0041(16) 0.0006(15)
 C36 0.0129(17) 0.031(2) 0.0217(19) -0.0039(16) 0.0025(15) 0.0002(15)
 C37 0.0198(19) 0.027(2) 0.028(2) 0.0005(17) 0.0075(17) 0.0018(16)
 C38 0.0184(19) 0.028(2) 0.030(2) 0.0026(17) 0.0033(17) 0.0050(16)
 C39 0.020(2) 0.040(2) 0.022(2) 0.0025(18) 0.0030(16) 0.0000(18)
 C40 0.0192(19) 0.032(2) 0.025(2) 0.0027(18) 0.0055(16) -0.0020(17)
 C42 0.027(2) 0.034(2) 0.043(3) 0.004(2) 0.010(2) 0.0060(18)
 C45 0.033(3) 0.041(3) 0.038(3) 0.009(2) 0.011(2) 0.003(2)
 C47 0.023(2) 0.037(2) 0.026(2) -0.0088(18) 0.0056(17) -0.0002(18)
 C48 0.030(2) 0.038(3) 0.051(3) 0.012(2) 0.018(2) 0.014(2)
 C49 0.039(3) 0.054(3) 0.047(3) 0.026(3) 0.011(2) 0.007(3)
 C51 0.0158(18) 0.028(2) 0.026(2) 0.0009(17) 0.0038(16) -0.0013(16)
 C59 0.040(3) 0.052(3) 0.062(4) 0.008(3) 0.022(3) 0.002(2)
 C66 0.042(3) 0.045(3) 0.074(4) 0.019(3) 0.033(3) 0.005(2)

C67 0.054(3) 0.044(3) 0.037(3) 0.013(2) 0.022(2) 0.019(3)
 C70 0.063(4) 0.068(4) 0.039(3) 0.022(3) -0.018(3) -0.029(3)
 O8 0.0215(14) 0.0315(16) 0.0224(14) -0.0032(12) 0.0073(12) 0.0020(12)
 O9 0.0144(14) 0.047(2) 0.0315(17) -0.0048(14) -0.0015(12) 0.0068(13)
 O11 0.0199(15) 0.064(2) 0.0273(16) 0.0012(16) 0.0106(13) -0.0023(15)
 O15 0.0243(16) 0.0387(18) 0.0402(18) 0.0009(15) 0.0164(14) 0.0039(13)
 O21 0.052(2) 0.0267(18) 0.068(3) 0.0067(17) 0.031(2) 0.0050(16)
 C13 0.0179(19) 0.032(2) 0.029(2) -0.0001(18) 0.0029(17) 0.0028(17)
 C24 0.0209(19) 0.024(2) 0.024(2) -0.0013(16) 0.0058(16) 0.0012(16)
 C35 0.0153(19) 0.039(2) 0.029(2) -0.0023(19) 0.0012(17) -0.0034(17)
 C46 0.058(3) 0.038(3) 0.048(3) 0.014(2) 0.021(3) 0.013(3)
 C52 0.049(3) 0.031(2) 0.029(2) 0.006(2) 0.011(2) 0.008(2)
 C55 0.038(3) 0.046(3) 0.026(2) -0.001(2) 0.003(2) 0.004(2)
 C71 0.056(4) 0.056(4) 0.060(4) 0.015(3) 0.022(3) -0.010(3)
 C73 0.057(4) 0.054(3) 0.027(2) 0.004(2) 0.002(2) 0.005(3)
 C72 0.060(4) 0.082(5) 0.049(4) 0.040(3) -0.013(3) -0.014(4)

_geom_special_details

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All esds (except the esd in the dihedral angle between two l.s. planes)
 are estimated using the full covariance matrix. The cell esds are taken
 into account individually in the estimation of esds in distances, angles
 and torsion angles; correlations between esds in cell parameters are only
 used when they are defined by crystal symmetry. An approximate (isotropic)
 treatment of cell esds is used for estimating esds involving l.s. planes.

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MOLECULAR GEOMETRY

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Br3 C47 1.888(4) . ?

Br4 C26 1.899(4) . ?

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O7 C24 1.374(5) . ?

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O14 C66 1.452(6) . ?

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O6 C20 C36 118.6(4) . . ?
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 Br4 C26 C27 C30 178.8(3) ?
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 C18 C29 C34 O5 -178.1(4) ?
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 Br4 C26 C38 C28 179.5(3) ?

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 O6 C20 C39 C17 -178.4(4) ?
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APPENDIX K: CHARACTERIZATION DATA AND JOB PLOT RATIOS FOR COMPOUND 6.6

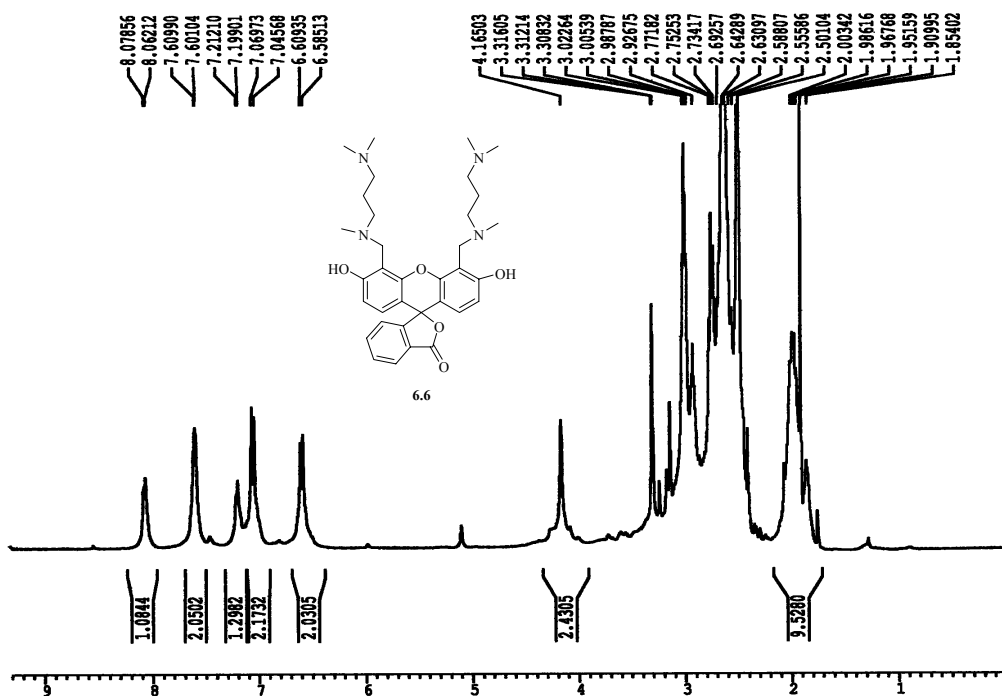


Figure K.1. ¹H NMR of compound 6.6

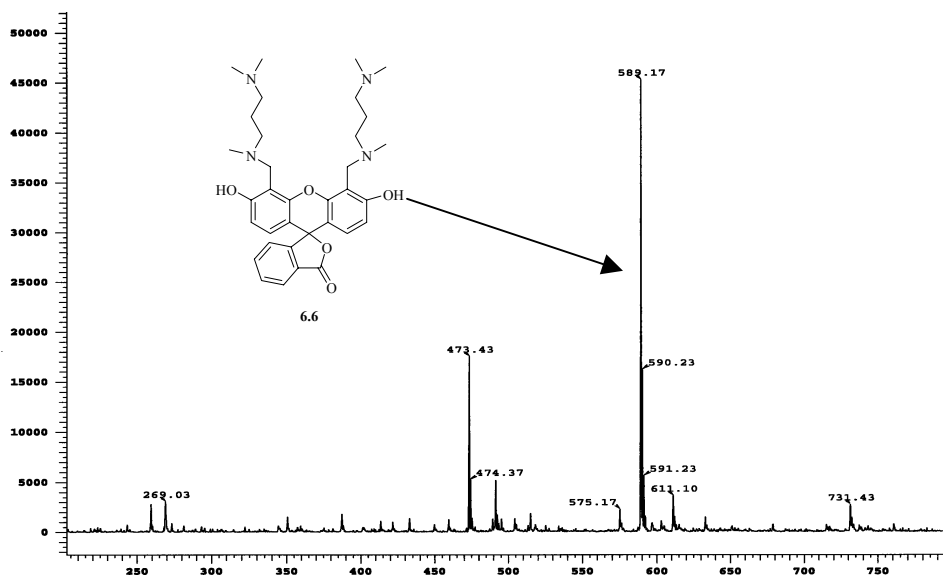


Figure K.1. MS of compound 6.6

Table K.1. Stoichiometry ratio of **6.6**-metal complexes

Dye	Metal	Stoichiometry Dye:Metal
Tetraamino Fluoresceine	Cu(II)	2:1
	Co(II)	1:1
	Zn(II)	1:1
	La(I)	2:1
	Mn(II)	1:2

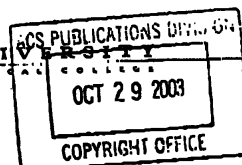
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Thank you for your consideration of this request.

Sincerely,

Nadia N. St. Luce
Phone: (225)-578-9096
Fax: (225)-578-3458
E-mail: nstluc1@lsu.edu

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10/10/03

VITA

Nadia Nadette Alexander was born in Roseau, Commonwealth of Dominica, on October 17, 1976. She grew up on Dominica with her mother Lucinthia St. Luce, father Pius St. Luce and brother Janah St. Luce. Her younger brother Kimo St. Luce was born in 1996.

In 1988 she moved to St. Thomas, United State Virgin Islands, where she attended Catholic High School from 1990-1994. In high school she was an active member of the National Honor Society, Close-Up Club, Spanish Club, and Assistant Editor of the School Yearbook. She graduated high school with honors. In the summer of 1994, following graduation, she attended the Summer Science Enrichment program where she was exposed to the many different fields of science and became interested in chemistry.

In the fall of 1994, she entered the University of the Virgin Islands on St. Thomas, USVI. While attending college she was a member of the Pre-Professional Science Club. In the fall of 1997 she was chosen to become a MARC Scholar. During the last two years of her college career, Nadia worked on synthesizing new ferrocene-bipyridine derivatives under the direction of Dr. Ralph Isovitsch. She completed her bachelor's degree in chemistry in May of 1999 and graduated with honors. That summer she was selected to supervise the Summer Science Enrichment program for the second time, having done so previously in the summer of 1998.

On August 10th 1999, she entered the graduate program in the Department of Chemistry at Louisiana State University. While at LSU Nadia synthesized and studied

novel chromophoric reagents for the detection of saccharides and amino acids under the direction of Dr. Robert M. Strongin. She was the treasurer of the Student Graduate Council from the fall of 2001 to spring 2002. She was the historian of the National Organization for the Professional Enhancement of Black Chemist Chemical Engineers, and a member of the American Chemical Society. Nadia is presently a candidate for the degree of Doctor of Philosophy in organic chemistry.